

# Elimination of Mother-to-Child HIV Transmission - Progress and Challenges

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National Institutes of Health

Department of Health and Human Services

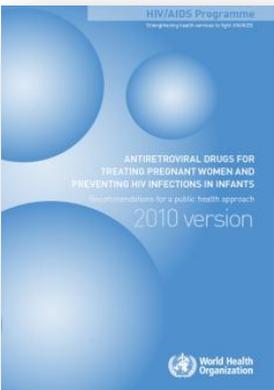


# Progress and Challenges in Preventing Perinatal HIV Infection

COUNTDOWN TO ZERO



- History interventions to prevent MTCT: 076 to present and progress in US
- Current WHO guidelines
- New goal of elimination of MTCT and improving maternal mortality
- Progress toward elimination MTCT
- Challenges and potential solutions



# Pediatric HIV Infection: Mother to Child Transmission

**MMWR**

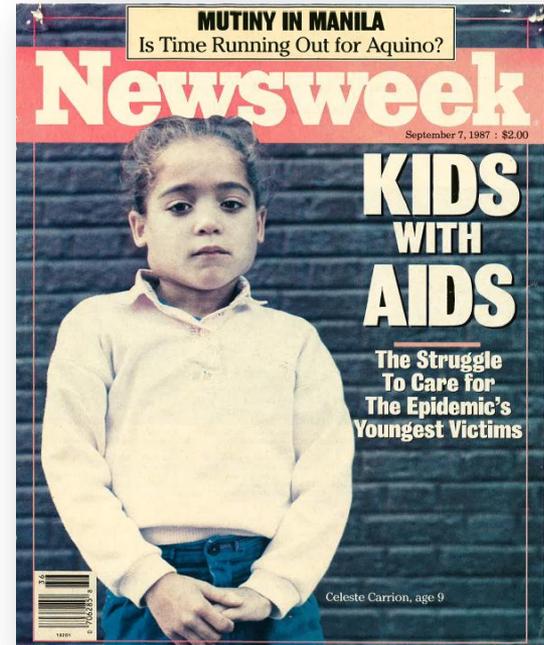
*Weekly*

December 17, 1982 / 31(49);665-667

**Unexplained Immunodeficiency and  
Opportunistic Infections in Infants --  
New York, New Jersey, California**

- It was quickly recognized most pediatric HIV infection occurred through transmission from mother to child although timing of transmission unclear.
- By 1994, more than 16,000 perinatally-infected children had been born in the U.S., with a critical need for prevention.

- The first case of pediatric AIDS was reported to the CDC in 1982, about 18 mos after the first case report in adults.



# Because Knowledge of Timing of MTCT Was Limited in 1992, the AZT Regimen in PACTG 076 Was Designed to Target Multiple Potential Time Points of Transmission

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## Pregnancy



AZT 100 mg  
5 times daily

**TARGET:**

*In Utero*

(after 1<sup>st</sup> trimester)

## Labor/Delivery



AZT IV 2 mg/kg  
➔ 1 mg/kg/hr

**TARGET:**

Intrapartum

## Infant



AZT 2 mg/kg  
q 6 hr x 6 weeks

**TARGET:**

Postpartum

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# 67% Reduction in Perinatal Transmission with PACTG 076 AZT Regimen

DSMB halted trial early in Feb 1994

## The New England Journal of Medicine

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Volume 331

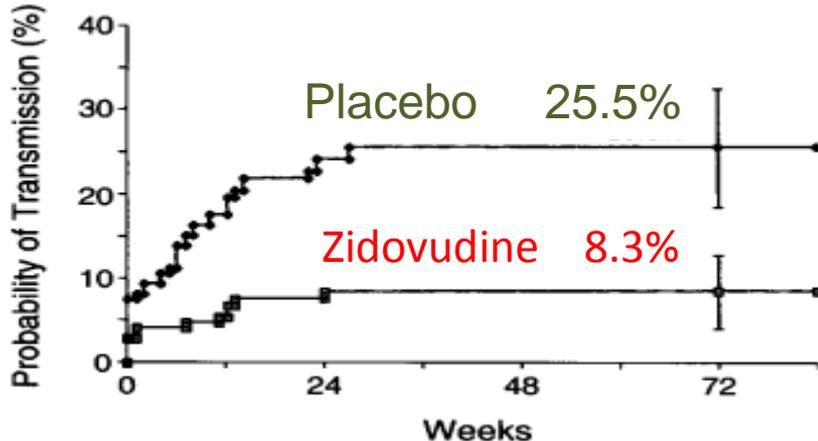
NOVEMBER 3, 1994

Number 18

### REDUCTION OF MATERNAL-INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

EDWARD M. CONNOR, M.D., RHODA S. SPERLING, M.D., RICHARD GELBER, Ph.D., PAVEL KISELEV, Ph.D., GWENDOLYN SCOTT, M.D., MARY JO O'SULLIVAN, M.D., RUSSELL VANDYKE, M.D., MOHAMMED BEY, M.D., WILLIAM SHEARER, M.D., Ph.D., ROBERT L. JACOBSON, M.D., ELEANOR JIMENEZ, M.D., EDWARD O'NEILL, M.D., BRIGITTE BAZIN, M.D., JEAN-FRANCOIS DELFRAISSY, M.D., MARY CULNANE, M.S., ROBERT COOMBS, M.D., Ph.D., MARY ELKINS, M.S., JACK MOYE, M.D., PAMELA STRATTON, M.D., AND JAMES BALSLEY, M.D., Ph.D.,

FOR THE PEDIATRIC AIDS CLINICAL TRIALS GROUP PROTOCOL 076 STUDY GROUP\*



CDC

August 5, 1994 / Vol. 43 / No. RR-11

**MMWR**

Recommendations  
and  
Reports

MORBIDITY AND MORTALITY WEEKLY REPORT

## Recommendations of the U.S. Public Health Service Task Force on the Use of Zidovudine to Reduce Perinatal Transmission of Human Immunodeficiency Virus

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Centers for Disease Control  
and Prevention (CDC)  
Atlanta, Georgia 30333





# Timing of Mother to Child HIV Transmission in Formula-Fed Populations

*In Formula-Fed Infants, Most HIV Transmission  
Occurs Around Delivery*

FORMULA-FEEDING POPULATION

Antenatal  
Early      Late



Overall cumulative risk  
perinatal HIV transmission  
(without antiretroviral  
drugs): 20-25%

While starting ARV drugs early in pregnancy is optimal, trials have shown that interventions started in late pregnancy, during labor or even given only to infant are also effective in preventing transmission



## How Do Antiretroviral Drugs Reduce Mother-to-Child HIV Transmission?

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- Lowering maternal blood/genital viral load
  - This mechanism likely most important in women with high viral load.
  - However, ARVs reduce transmission with low viral load and are effective even when no ARVs during pregnancy.

- Two other important mechanisms through which ARVs reduce transmission:



- *Pre-exposure prophylaxis* of infant (through transplacental drug passage).



- *Post-exposure prophylaxis* of infant (through continued drug after birth).



# PMTCT Strategies in the US

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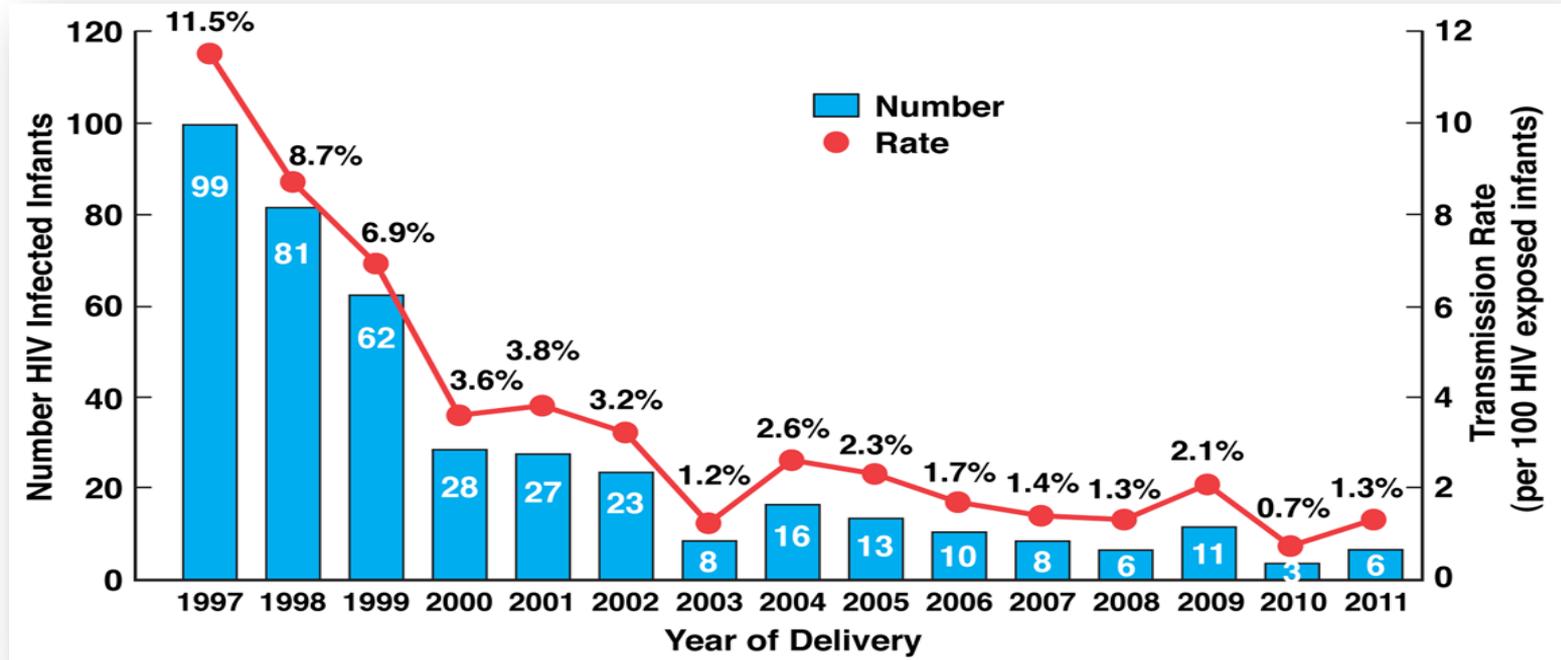


- Universal prenatal HIV testing of all pregnant women
- Use of combination antiretroviral drugs during pregnancy to rapidly and durably suppress viral load
  - Individualized, laboratory-guided patient management (HIV RNA, CD4)
- Infant antiretroviral prophylaxis
- Elective caesarean section (if RNA >1,000 c/mL)
- Replacement feeding

# Research to Implementation:

## Number of HIV-Infected Infants and MTCT Rate in New York State by Year of Delivery, 1997-2011

1990: N=475, MTCT ~25%

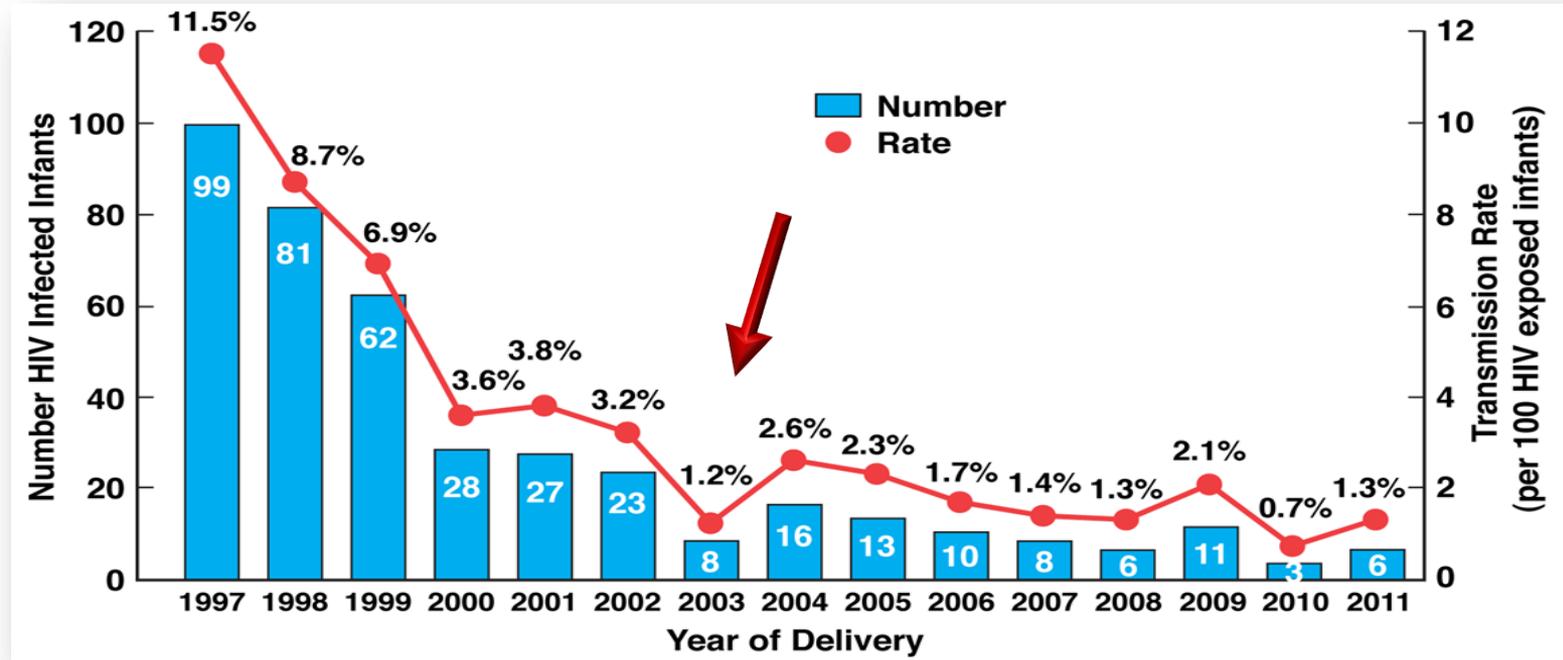


Source: AIDS Institute, New York State Department of Health, 2012

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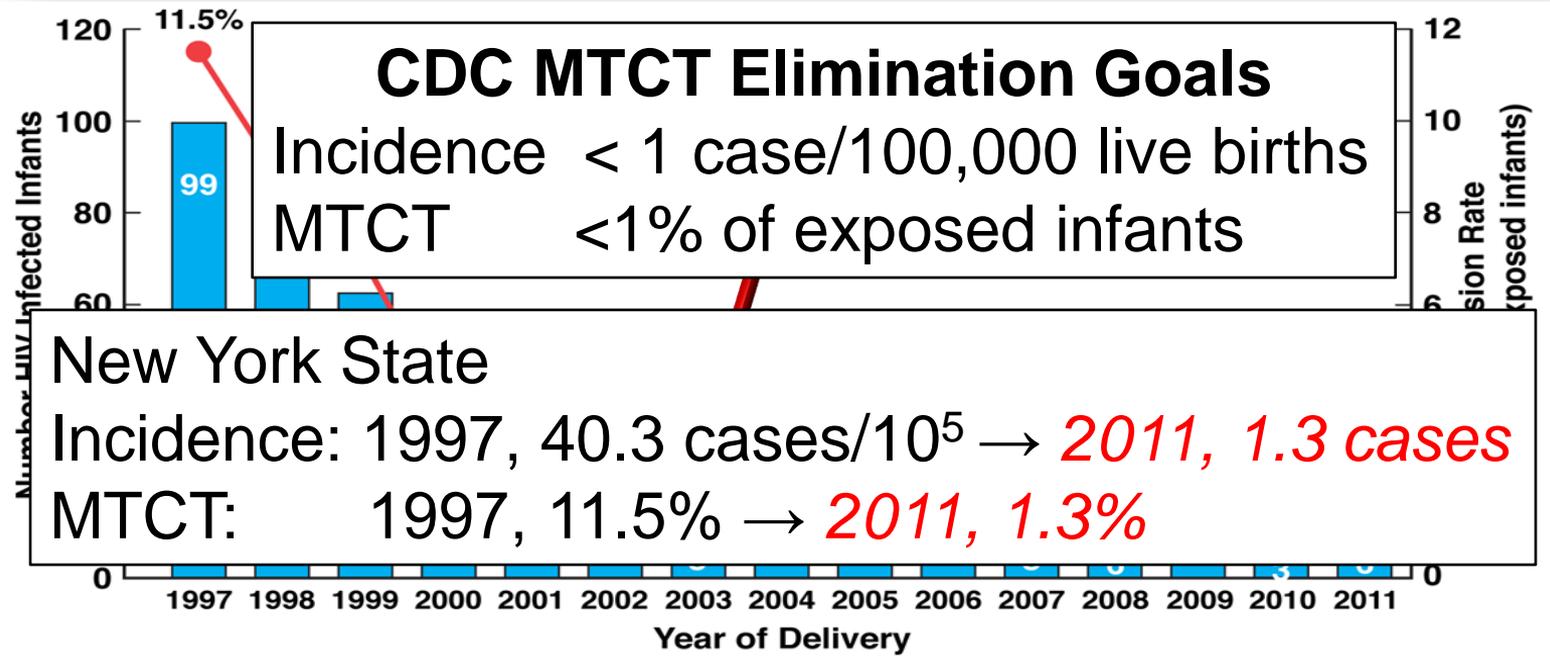


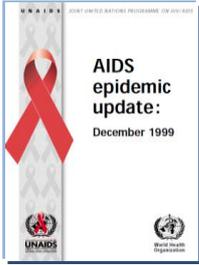
Source: AIDS Institute, New York State Department of Health, 2012

# Research to Implementation:

## Number of HIV-Infected Infants and MTCT Rate in New York State by Year of Delivery, 1997-2011

1990: N=475, MTCT ~25%





# Global HIV Epidemic in Children

- After 1994, as interventions to prevent MTCT in resource-rich countries began to be implemented, attention turned to the developing world, where most pediatric HIV infections were occurring.

## Global summary of the HIV/AIDS epidemic, December 1999

People newly infected with HIV in 1999	<b>Total</b>	<b>5.6 million</b>
	Adults	5 million
	Women	2.3 million
	Children <15 years	570 000
Number of people living with HIV/AIDS	<b>Total</b>	<b>33.6 million</b>
	Adults	32.4 million
	Women	14.8 million
	Children <15 years	1.2 million
AIDS deaths in 1999	<b>Total</b>	<b>2.6 million</b>
	Adults	2.1 million
	Women	1.1 million
	Children <15 years	470 000
Total number of AIDS deaths since the beginning of the epidemic	<b>Total</b>	<b>16.3 million</b>
	Adults	12.7 million
	Women	6.2 million
	Children <15 years	3.6 million

- In 1999, an estimated 570 000 children aged 14 or younger became infected with HIV. Over 90% were babies born to HIV-positive women, who acquired the virus at birth or through their mother's breastmilk. Of these, almost nine-tenths were in sub-Saharan Africa.

# Post-076 Clinical Trials of PMTCT in Resource-Limited Countries

*Evolution of PMTCT Trials: Shorter Regimens to Decrease AP-IP MTCT*

**1994**

**2004**

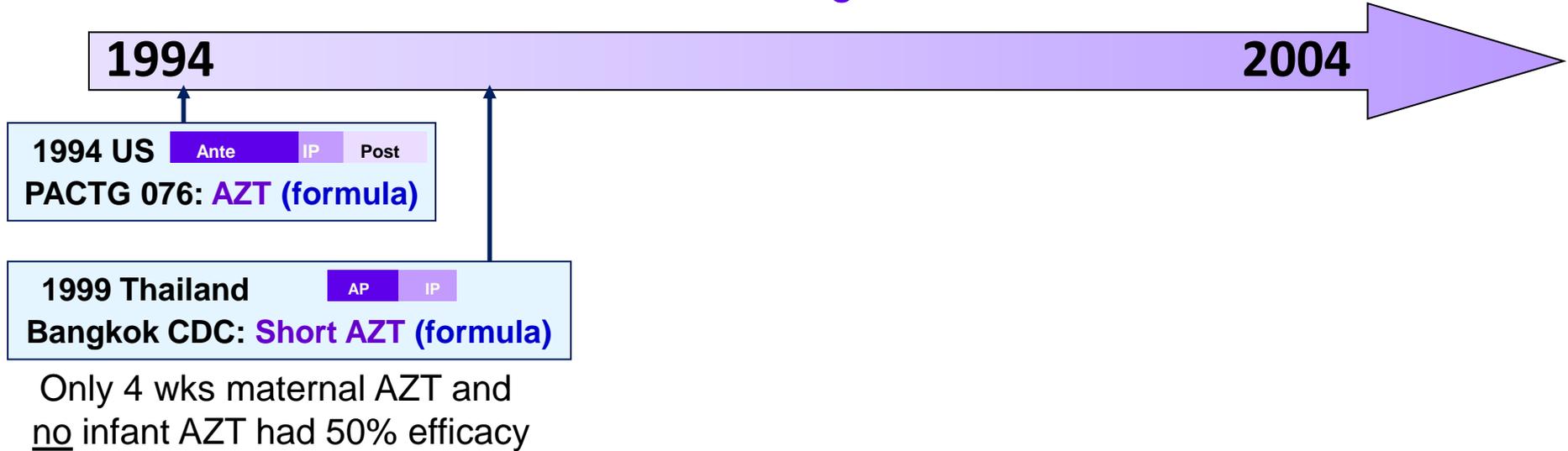
1994 US **Ante** IP Post

PACTG 076: **AZT (formula)**



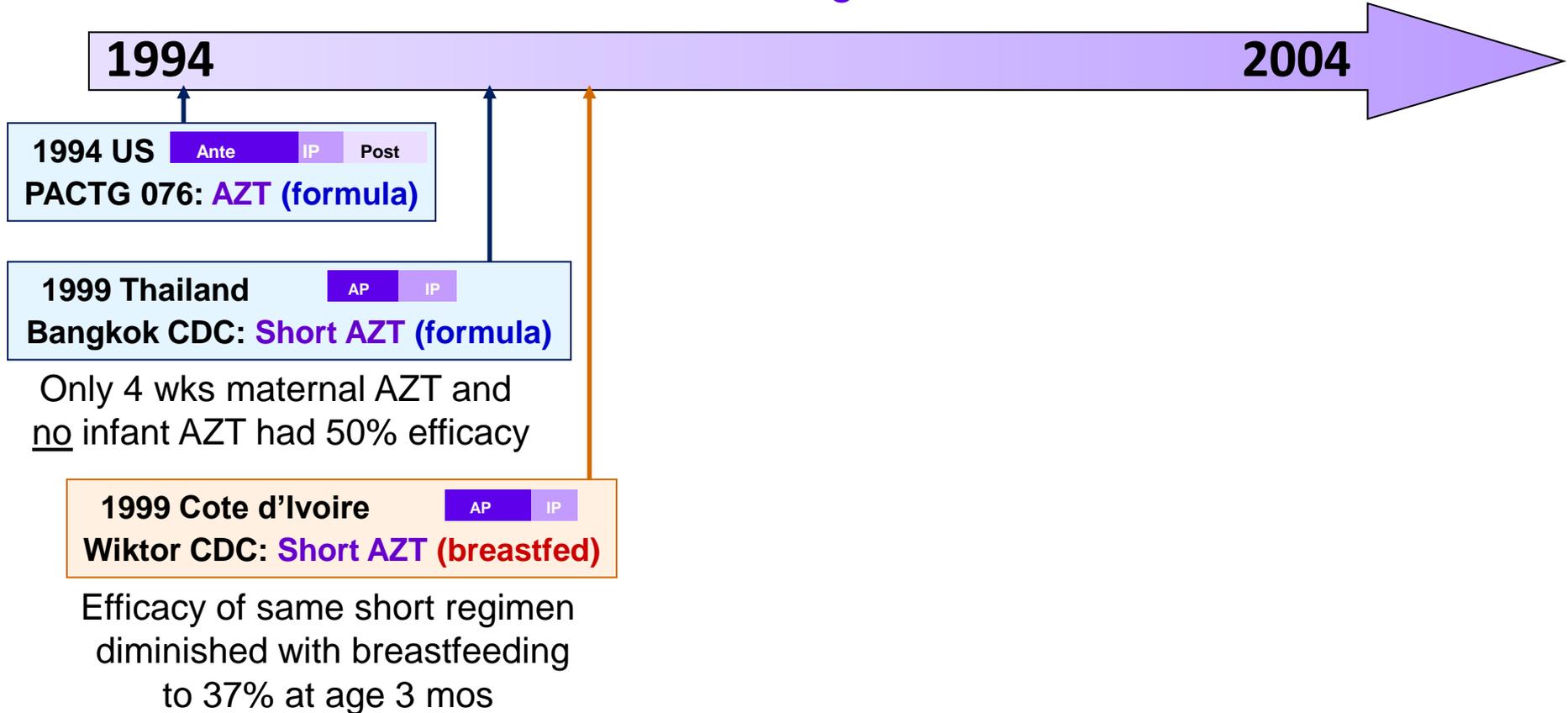
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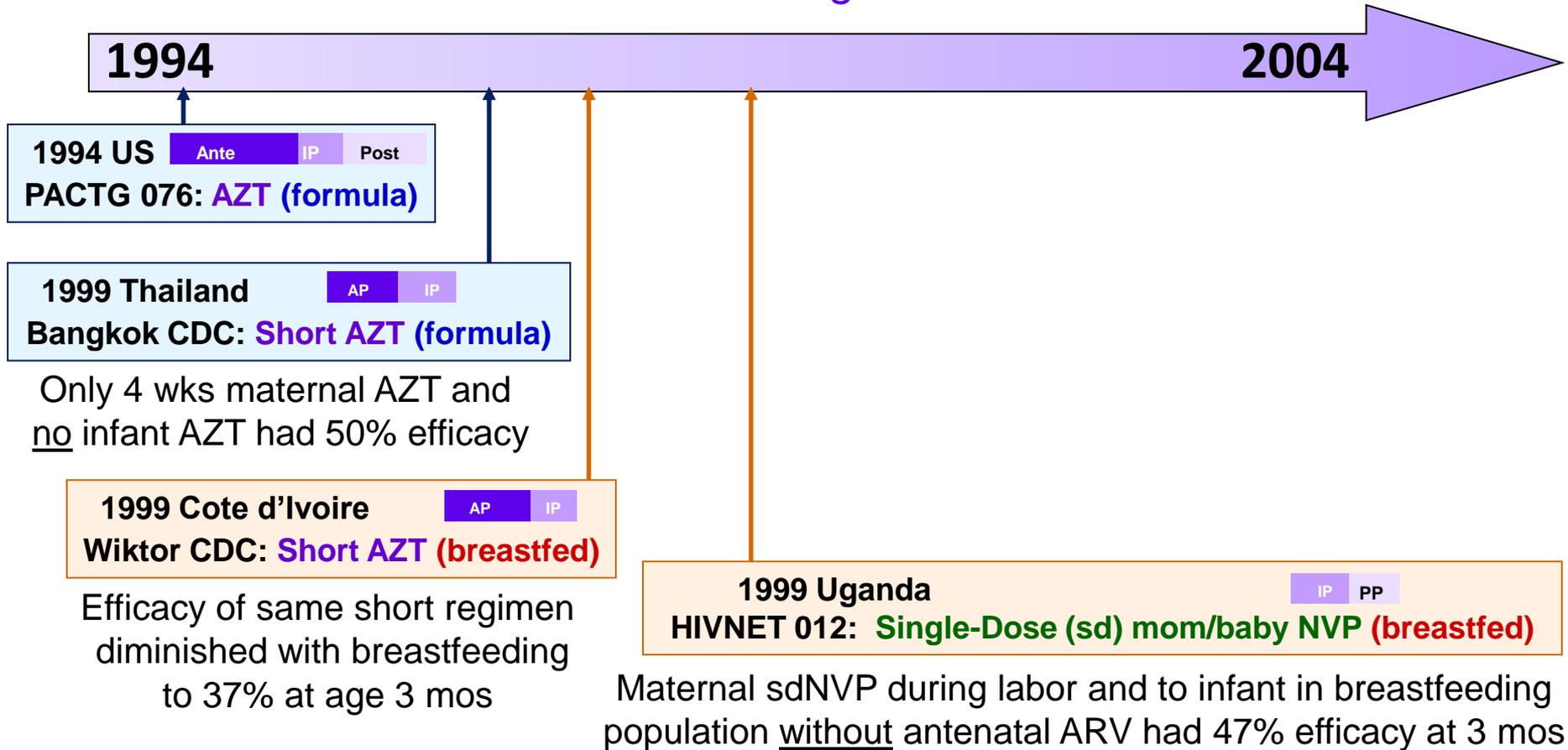
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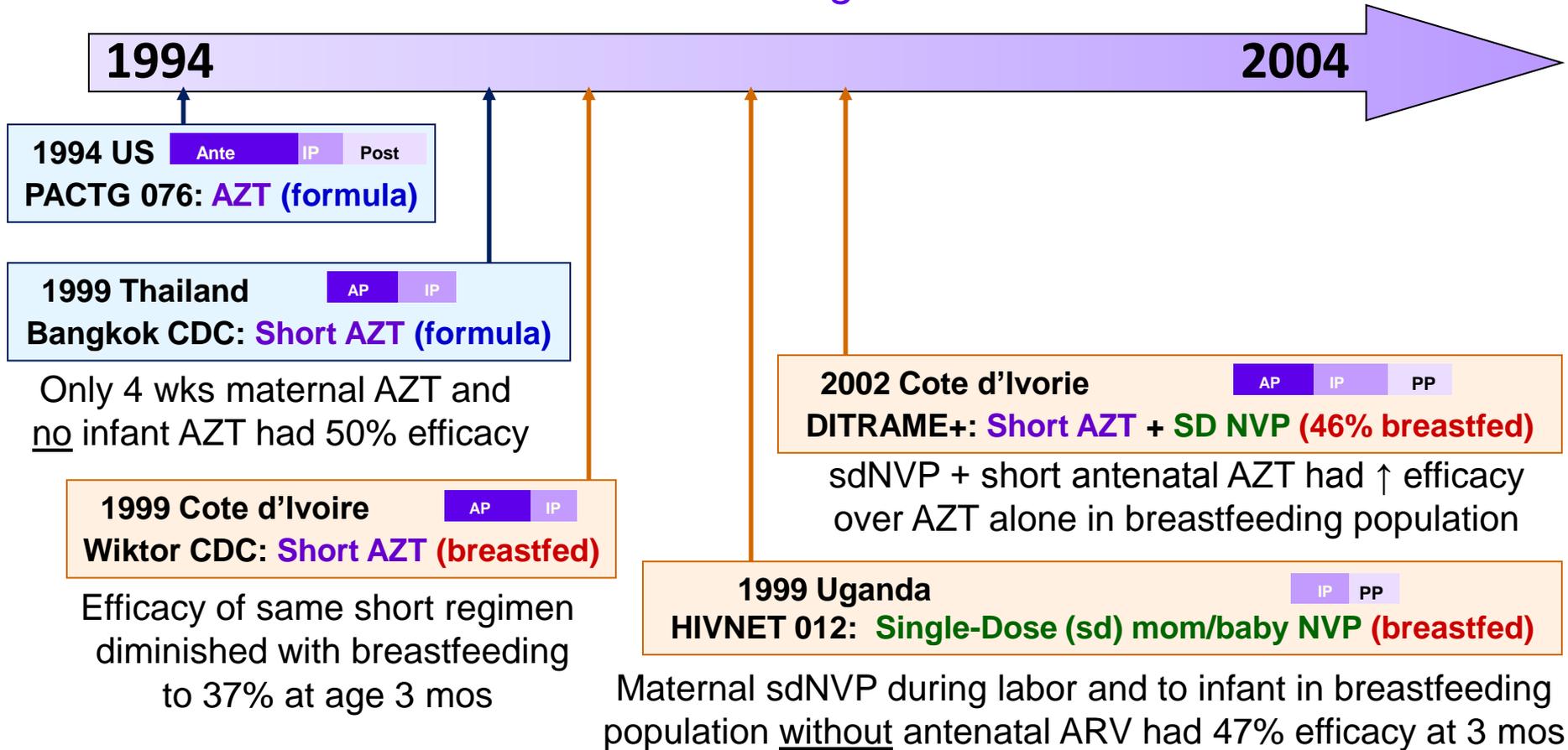
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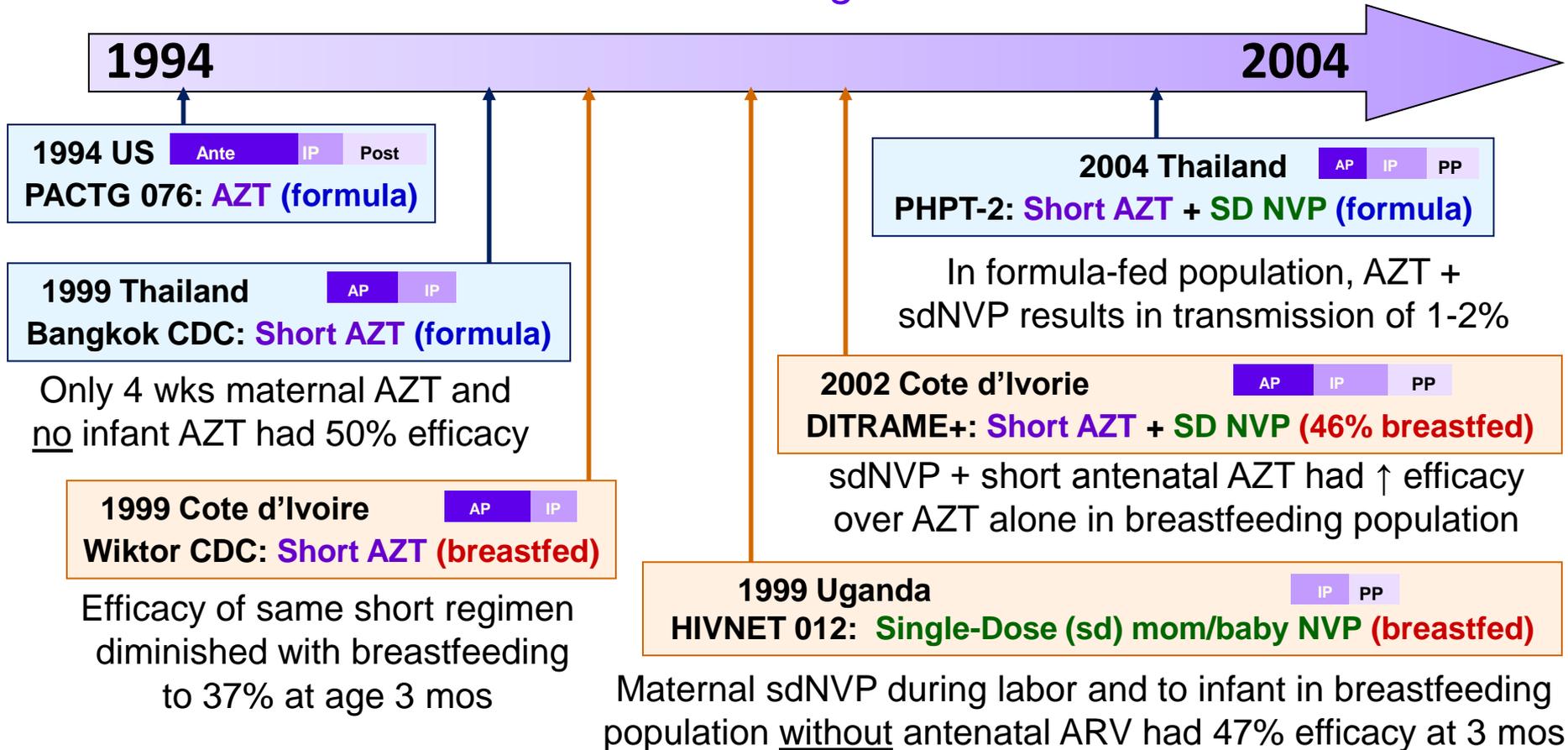
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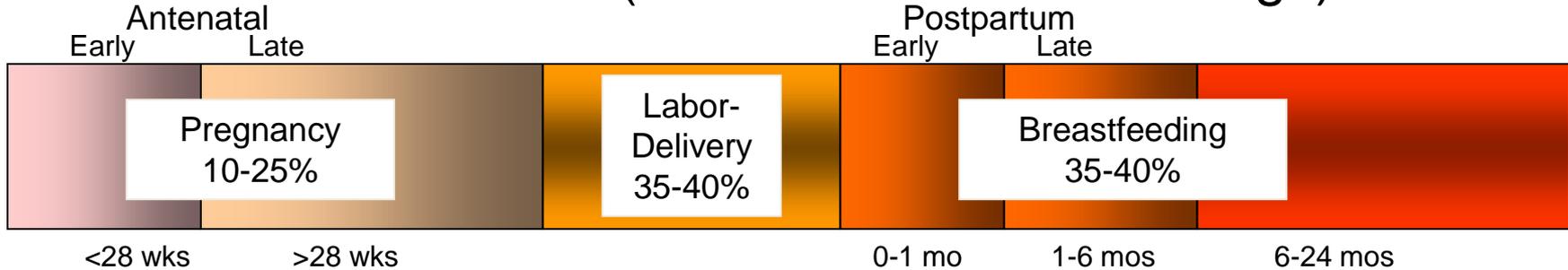


# Timing of Mother to Child HIV Transmission

## *Doubling of Transmission Risk with Prolonged Breastfeeding*

BREASTFEEDING POPULATION

Overall cumulative risk MTCT  
(without antiretroviral drugs): 40-45%



Since breastfeeding is the cornerstone of infant survival in many resource-limited countries but is associated with high rates of HIV transmission, development of interventions to allow safe breastfeeding was critical

# Clinical Trials of Prevention of Postnatal Mother to Child Transmission

**2003**

**2010**

**2003 Africa**

**SIMBA: Infant ARV**

Observational; 6 mos infant  
ARV (daily NVP or 3TC) had  
low postnatal MTCT

# Clinical Trials of Prevention of Postnatal Mother to Child Transmission

**2003**

**2010**

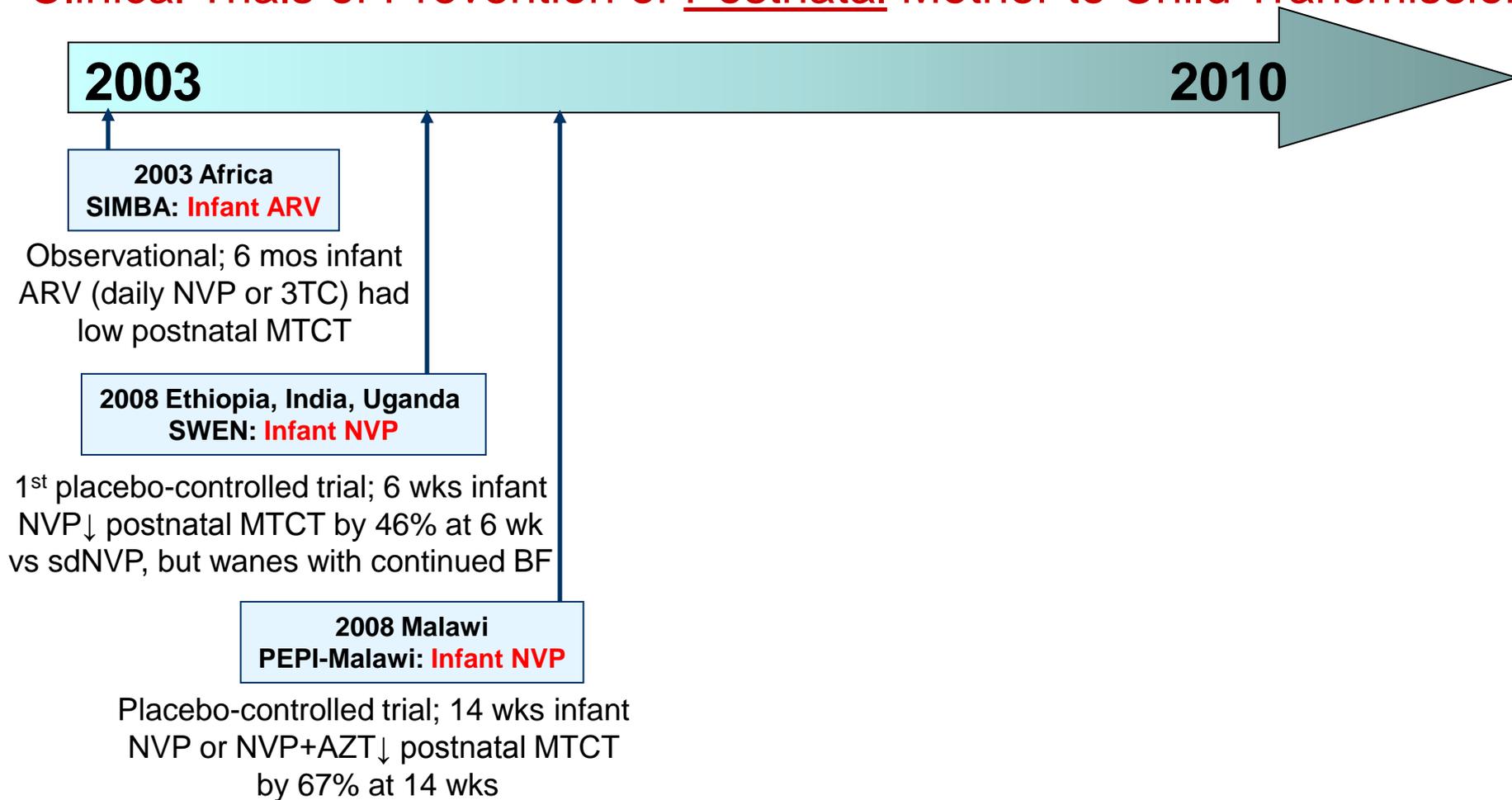
**2003 Africa**  
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Observational; 6 mos infant ARV (daily NVP or 3TC) had low postnatal MTCT

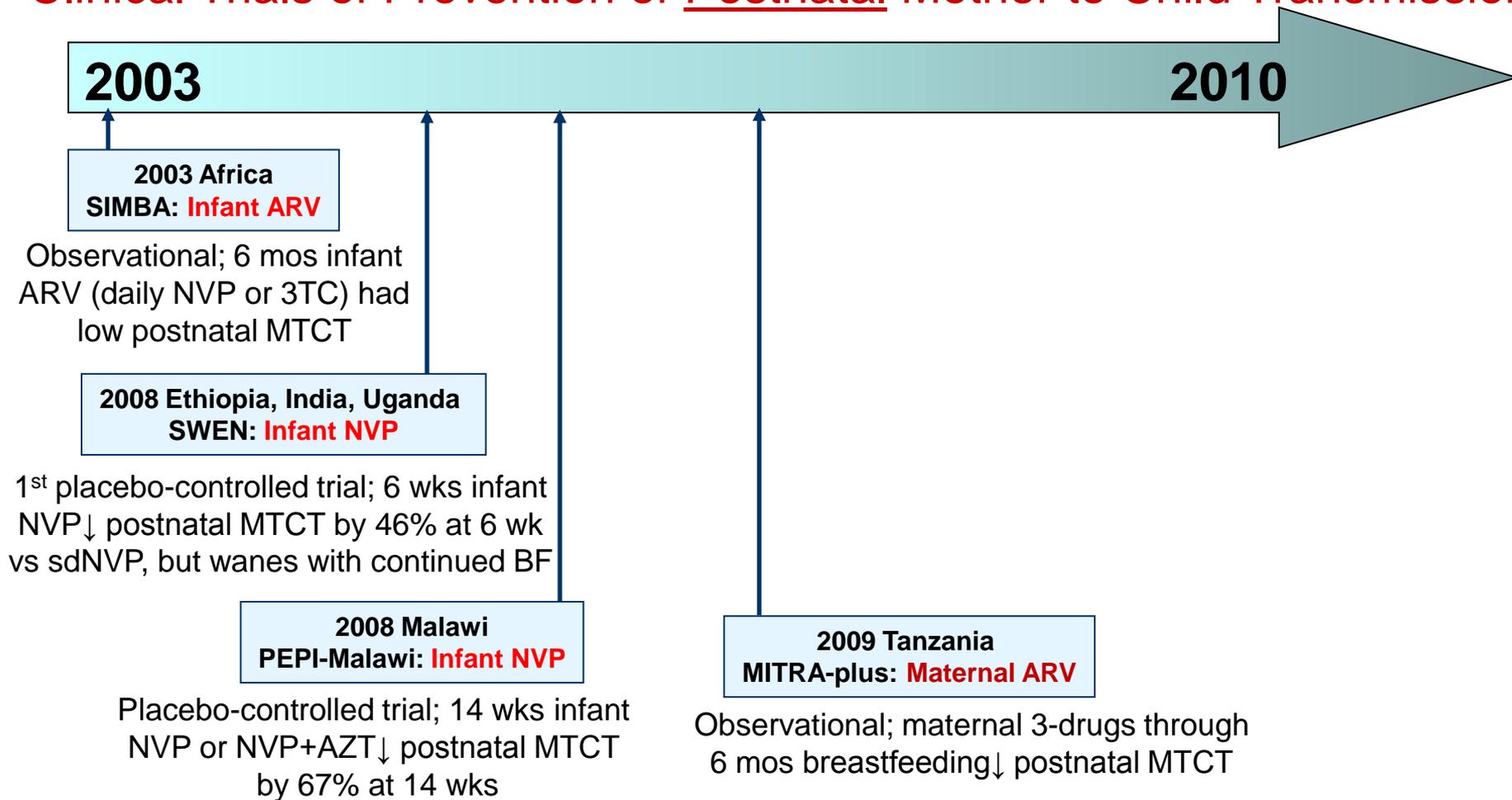
**2008 Ethiopia, India, Uganda**  
**SWEN: Infant NVP**

1<sup>st</sup> placebo-controlled trial; 6 wks infant NVP ↓ postnatal MTCT by 46% at 6 wk vs sdNVP, but wanes with continued BF

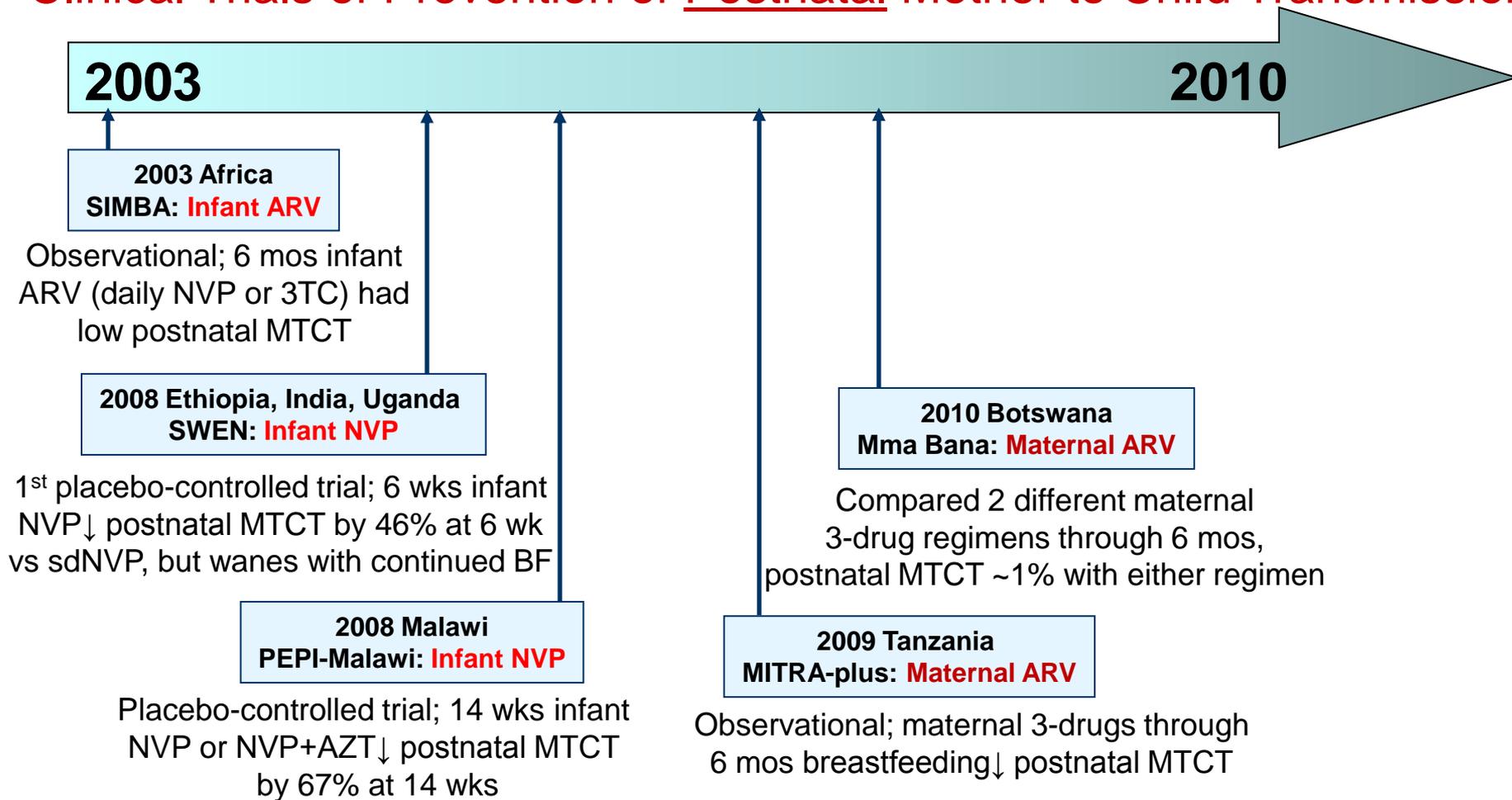
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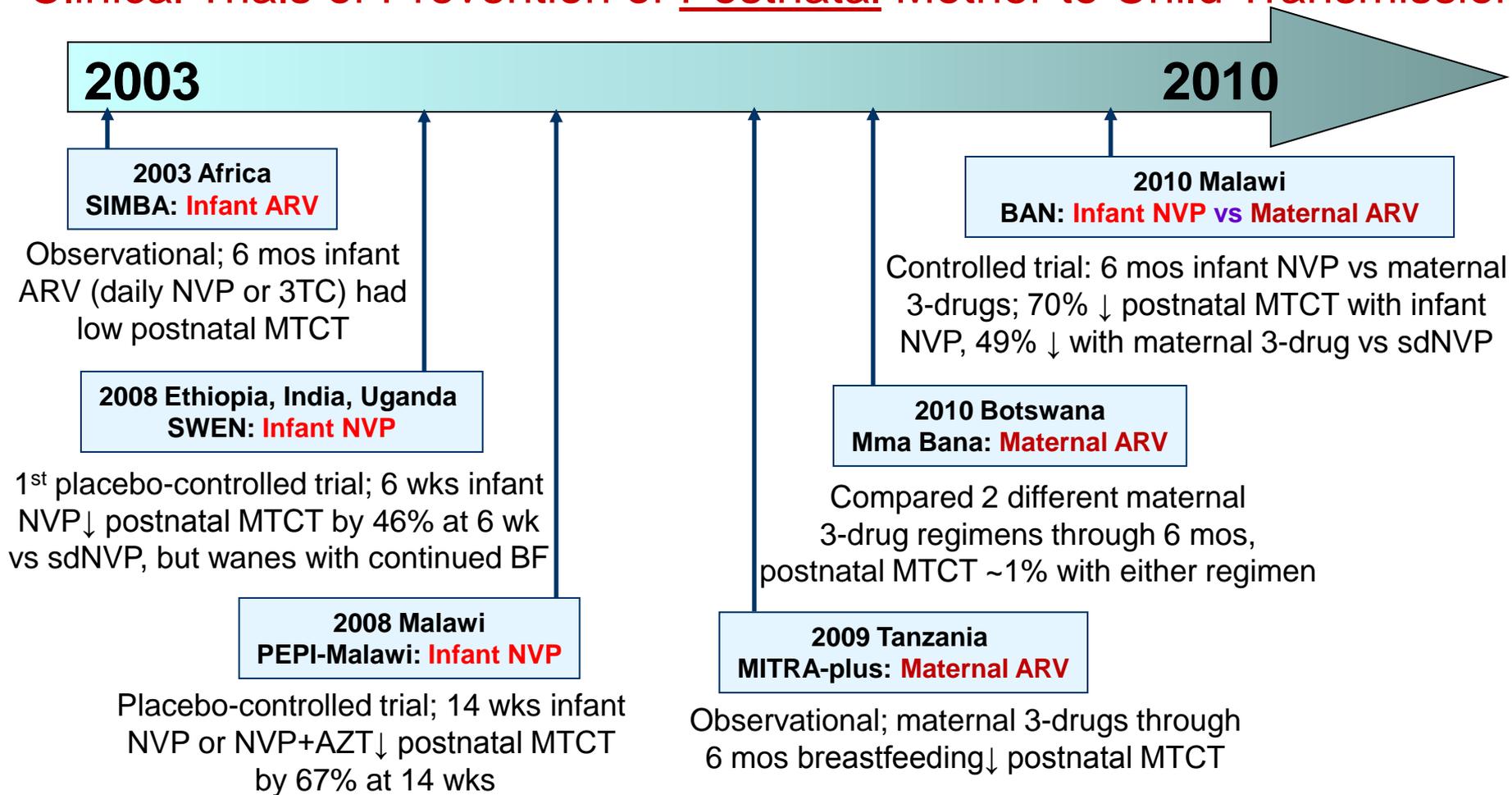
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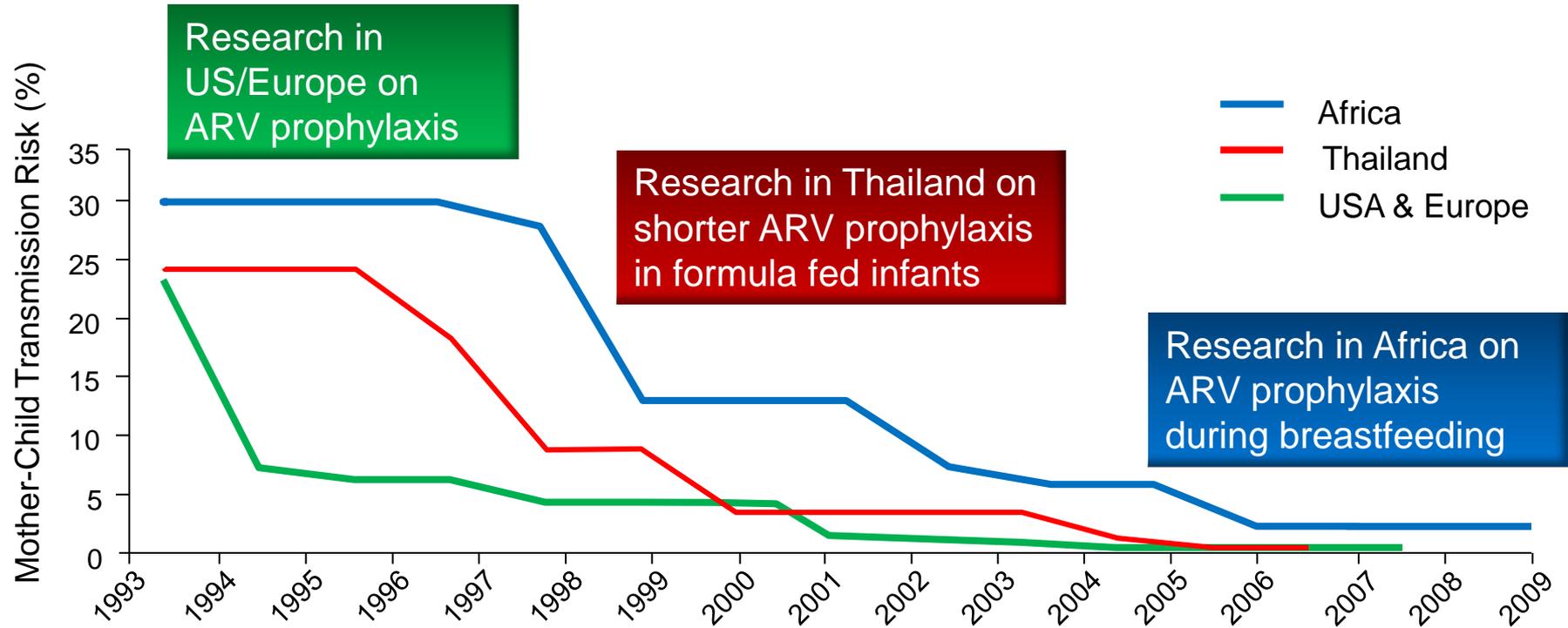
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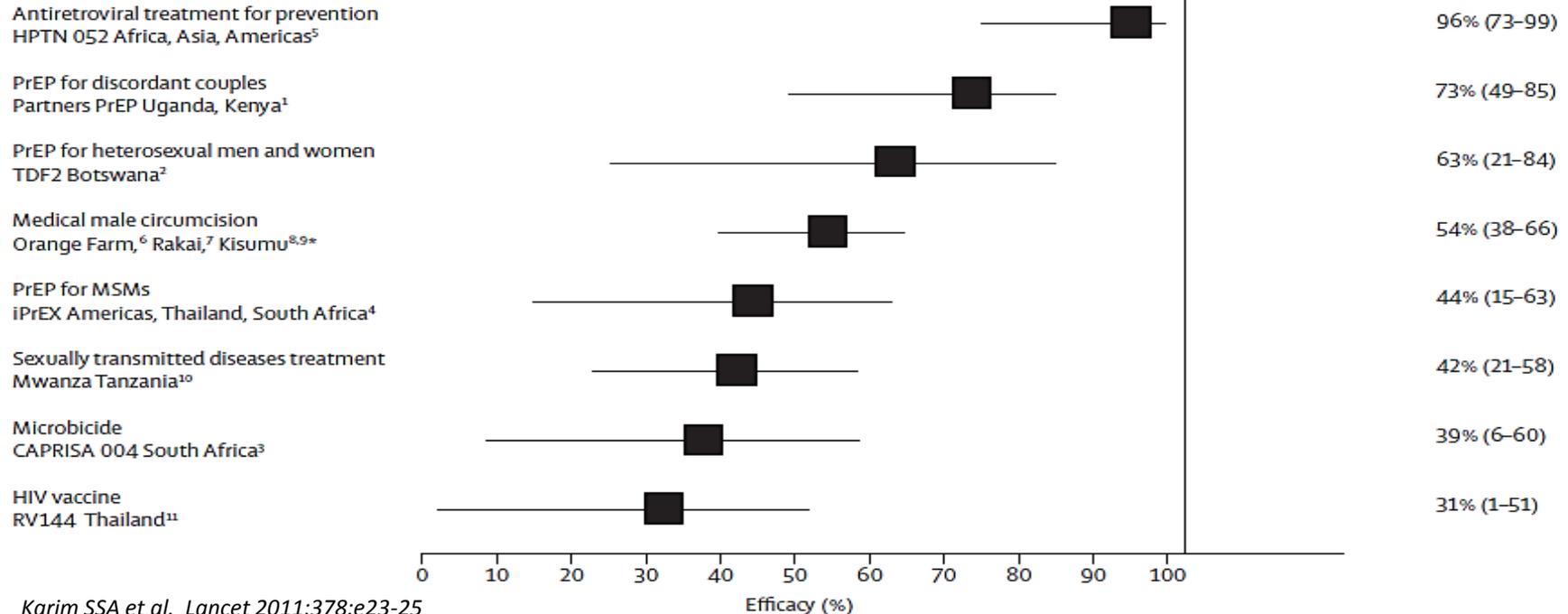
# International Research Has Enabled Optimizing PMTCT Interventions



Source: adapted from N. Shaffer, WHO, 2010/RJ Simonds 2012

# Of Prevention Technologies Effective in Reducing HIV Transmission

## PMTCT is One of Most Effective Interventions



# Of Prevention Technologies Effective in Reducing HIV Transmission

## PMTCT is One of Most Effective Interventions

### AZT alone - PACTG 076 (8.3% vs 25.5%, Connor NEJM 1994)

Antiretroviral treatment for prevention  
HPTN 052 Africa, Asia, Americas<sup>5</sup>

PrEP for discordant couples  
Partners PrEP Uganda, Kenya<sup>1</sup>

PrEP for heterosexual men and women  
TDF2 Botswana<sup>2</sup>

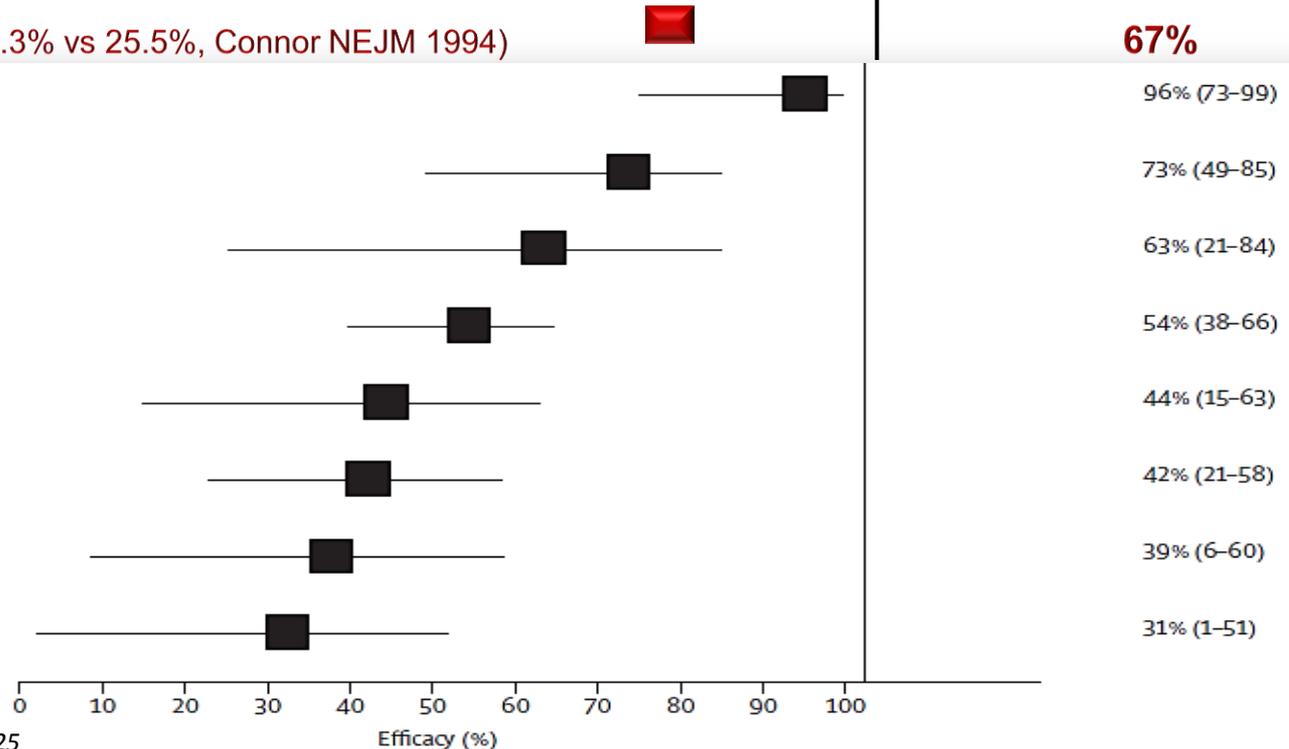
Medical male circumcision  
Orange Farm,<sup>6</sup> Rakai,<sup>7</sup> Kisumu<sup>8,9\*</sup>

PrEP for MSMs  
iPrEX Americas, Thailand, South Africa<sup>4</sup>

Sexually transmitted diseases treatment  
Mwanza Tanzania<sup>10</sup>

Microbicide  
CAPRISA 004 South Africa<sup>3</sup>

HIV vaccine  
RV144 Thailand<sup>11</sup>



# Of Prevention Technologies Effective in Reducing HIV Transmission

## PMTCT is One of Most Effective Interventions

**AZT/sdNVP vs AZT alone - PHPT-2 (1.1% vs 6.2%, Lallemand NEJM 2004)**



**82%**

**AZT alone - PACTG 076 (8.3% vs 25.5%, Connor NEJM 1994)**



**67%**

Antiretroviral treatment for prevention  
HPTN 052 Africa, Asia, Americas<sup>5</sup>

96% (73–99)

PrEP for discordant couples  
Partners PrEP Uganda, Kenya<sup>1</sup>

73% (49–85)

PrEP for heterosexual men and women  
TDF2 Botswana<sup>2</sup>

63% (21–84)

Medical male circumcision  
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54% (38–66)

PrEP for MSMs  
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44% (15–63)

Sexually transmitted diseases treatment  
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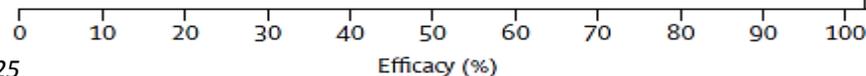
42% (21–58)

Microbicide  
CAPRISA 004 South Africa<sup>3</sup>

39% (6–60)

HIV vaccine  
RV144 Thailand<sup>11</sup>

31% (1–51)



# Of Prevention Technologies Effective in Reducing HIV Transmission

## PMTCT is One of Most Effective Interventions

**Option A vs No ARV S Africa** (1.5% vs 22%, Dinh 2011 IAS; Rundare 2012 CROI) 

**93%**

**AZT/sdNVP vs AZT alone - PHPT-2** (1.1% vs 6.2%, Lallemand NEJM 2004) 

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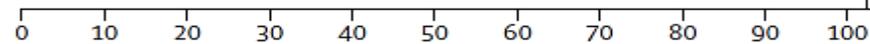
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HIV vaccine  
RV144 Thailand<sup>11</sup>

31% (1-51)



Efficacy (%)

# Of Prevention Technologies Effective in Reducing HIV Transmission

## PMTCT is One of Most Effective Interventions

**cART vs No ARV (076 placebo)** (0.8% vs 25.5%, US/Europe 2006)

**Option A vs No ARV S Africa** (1.5% vs 22%, Dinh 2011 IAS; Rundare 2012 CROI)

**AZT/sdNVP vs AZT alone - PHPT-2** (1.1% vs 6.2%, Lallemand NEJM 2004)

**AZT alone - PACTG 076** (8.3% vs 25.5%, Connor NEJM 1994)

**97%**

**93%**

**82%**

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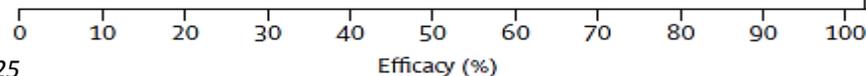
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# 2010 WHO Guidelines: Public Health Approach to PMTCT

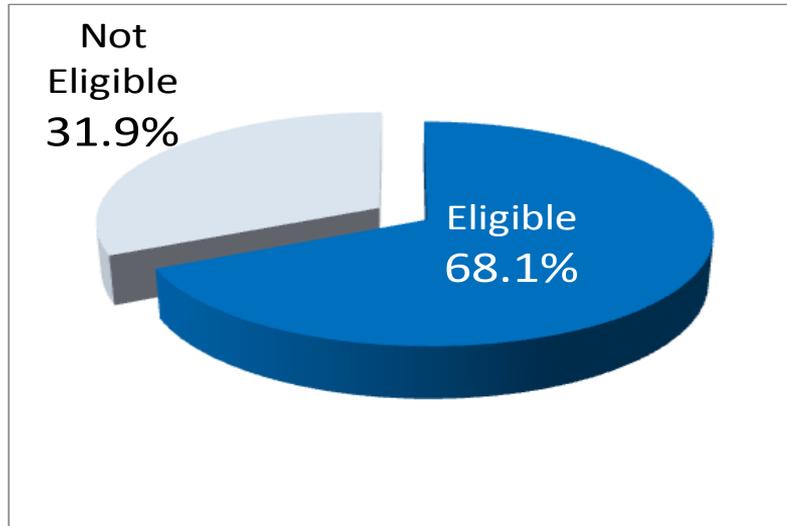
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- Shift to use of multi-drug efficacious regimens
  - sd-NVP no longer recommended regimen
- Emphasized the importance of identifying and treating ART-eligible women
- Extended ARV coverage through duration of exposure
  - Prophylaxis initiated at 14 wks
  - ARV to mother or infant during breastfeeding
- Endorsed breast feeding as preferred method, with ARV coverage



# Women Eligible for ART Are At Highest Risk for Mother to Child HIV Transmission and Mortality

*Kuhn L et al. AIDS 2010;24:1374-7*

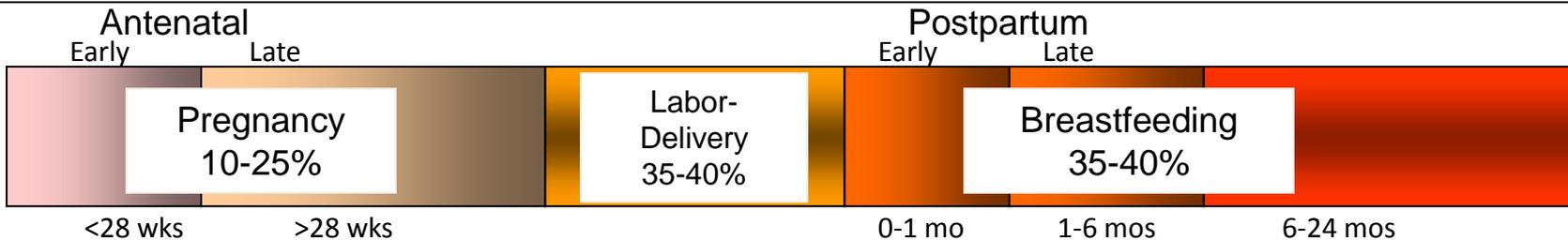


	Eligible for ART	Not eligible for ART
MTCT by 6 wk	16.7%	5.0%
Proportion of MTCT by 6 wks	87.5%	12.5%
MTCT after 6 wks	17.0%	4.2%
Proportion of MTCT after 6 wks	87.5%	12.5%
Maternal mortality 24 mo post delivery	92%	8%

- Cohort 1,025 pregnant women Zambia prior to ART availability
- Analyzed MTCT/mortality by eligibility for ART with current WHO criteria (CD4 <350 or WHO Stage 3 or 4)



# 2010 WHO Guidelines

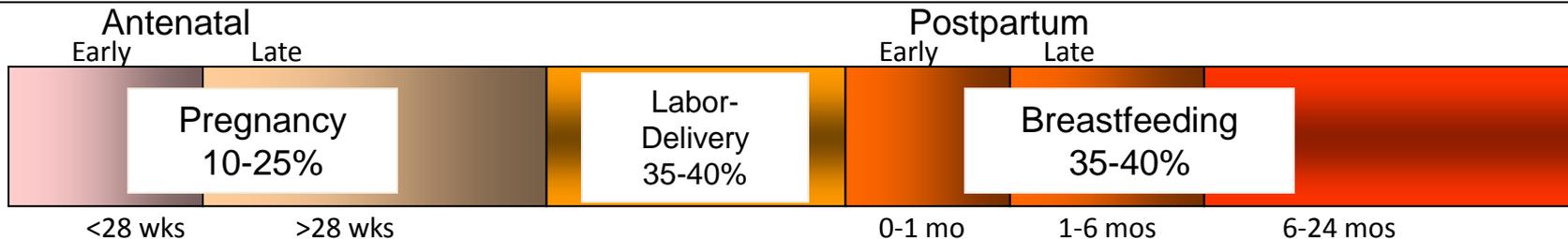


~40-50%

Maternal lifelong ARV Therapy (CD4<350, WHO 3, 4)



# 2010 WHO Guidelines



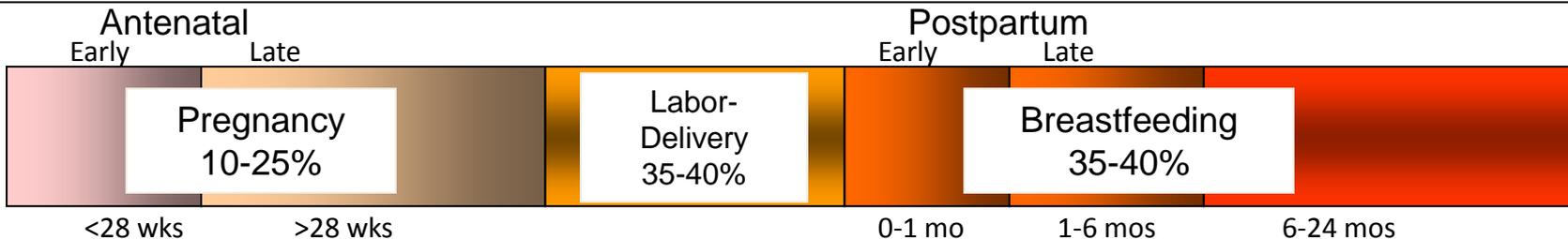
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Maternal lifelong ARV Therapy (CD4<350, WHO 3, 4)

Time-Limited Provision of ARV Prophylaxis if CD4 >350 and WHO Stage 1/2 to Prevent MTCT



# 2010 WHO Guidelines



**~40-50%** Maternal lifelong ARV Therapy (CD4 < 350, WHO 3, 4)

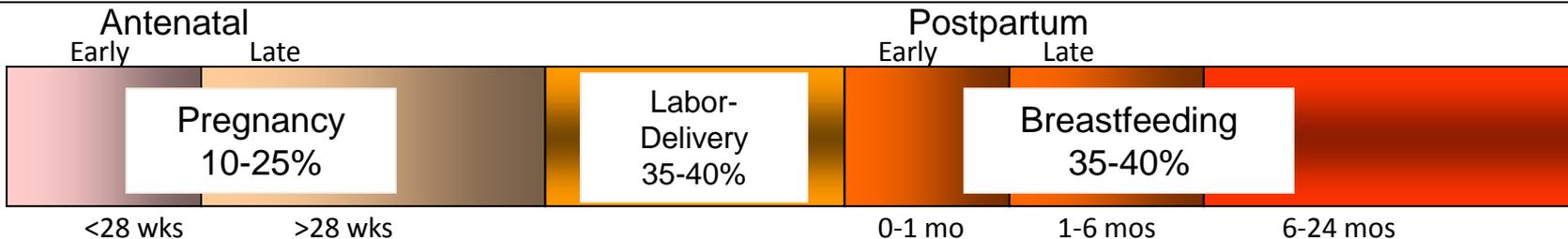
Time-Limited Provision of ARV Prophylaxis if CD4 > 350 and WHO Stage 1/2 to Prevent MTCT

Starting 14 wks

**Option A** AZT + sdNVP (+ tail) Daily Infant NVP x12 mos



# 2010 WHO Guidelines



**~40-50%** Maternal lifelong ARV Therapy (CD4 < 350, WHO 3, 4)

Time-Limited Provision of ARV Prophylaxis if CD4 > 350 and WHO Stage 1/2 to Prevent MTCT

Starting 14 wks

**Option A** AZT + sdNVP (+ tail) | Daily Infant NVP x12 mos

**Option B** Maternal Triple Drug Prophylaxis through 12 mos

Infant ZDV or NVP for 4-6 wks



# 2010 WHO Guidelines



Antenatal  
Early Late

Postpartum  
Early Late

- Full Option A vs B have not been compared in trial (there is ongoing trial) but available data indicate both Options have similar efficacy for PMTCT in women with high CD4:
  - In utero MTCT ~1.7% with maternal triple ARV vs AZT/sdNVP when maternal CD4 350-500  
(Kesho Bora, deVincenzi I et al. *Lancet Inf Dis* 2011;11:171-80)
  - Postpartum MTCT ~2-3% with maternal triple ARV vs infant NVP when maternal CD4 >250  
(BAN, Chasela C et al. *NEJM* 2010;362:2271-81)

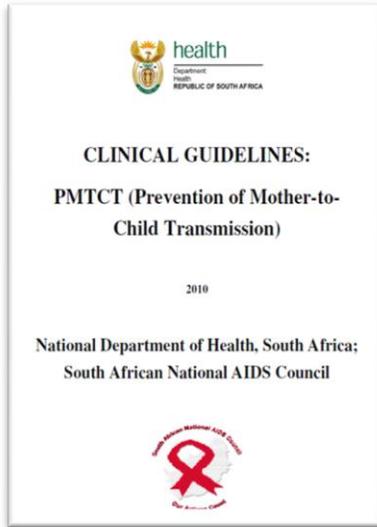
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# PMTCT Program Implementation in South Africa



# Comparison 2008 and 2010 South Africa National PMTCT Guidelines

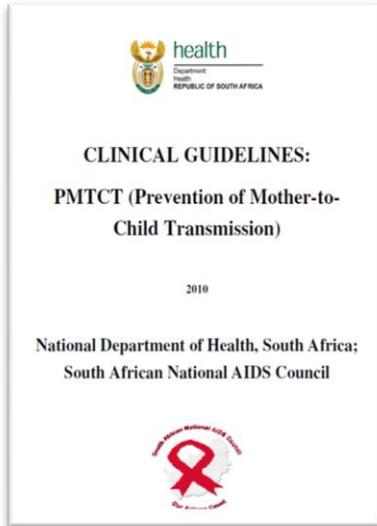
Rundare A et al. 19<sup>th</sup> CROI, Seattle, WA March 2012 (Abs 1003)



- In 2010, S. African guidelines implemented Option A (AZT/sdNVP + infant NVP) & ART with CD4 <350.
- 1,995 mother-infant pairs followed June 2009-2011:
  - 1147 (57.5%) attended ANC before 2010 (AZT/sdNVP, no infant prophylaxis)
  - 848 (42.5%) attended ANC after 2010 (Option A)

# Comparison 2008 and 2010 South Africa National PMTCT Guidelines

Rundare A et al. 19<sup>th</sup> CROI, Seattle, WA March 2012 (Abs 1003)



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- 1,995 mother-infant pairs followed June 2009-2011:
  - 1147 (57.5%) attended ANC before 2010 (AZT/sdNVP, no infant prophylaxis)
  - 848 (42.5%) attended ANC after 2010 (Option A)
- 6 week MTCT rates significantly lower with new guidelines:
  - Historical MTCT at 6 weeks with no ARV: 17-22%
  - Before new guidelines (AZT/sdNVP): 3.4% (95% CI 2.6-5.0%)
  - After new guidelines (add infant NVP): 1.5% (95% CI 0.9-2.9%)

Believe it.  
.....  
Do it.



Based on new  
PMTCT trial  
successes, WHO set  
a new goal to  
virtually eliminate  
new pediatric HIV  
infections and  
improve maternal  
survival by 2015

GLOBAL PLAN TOWARDS THE ELIMINATION OF NEW HIV INFECTIONS  
AMONG CHILDREN BY 2015 AND KEEPING THEIR MOTHERS ALIVE

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# COUNTDOWN TO ZERO

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Global plan towards the elimination of new HIV infections in children and keeping their mothers alive.

**Global Target #1: Reduce the number of new HIV infections among children by 90%**

**Global Target #2: Reduce the number of AIDS-related maternal deaths by 50%**

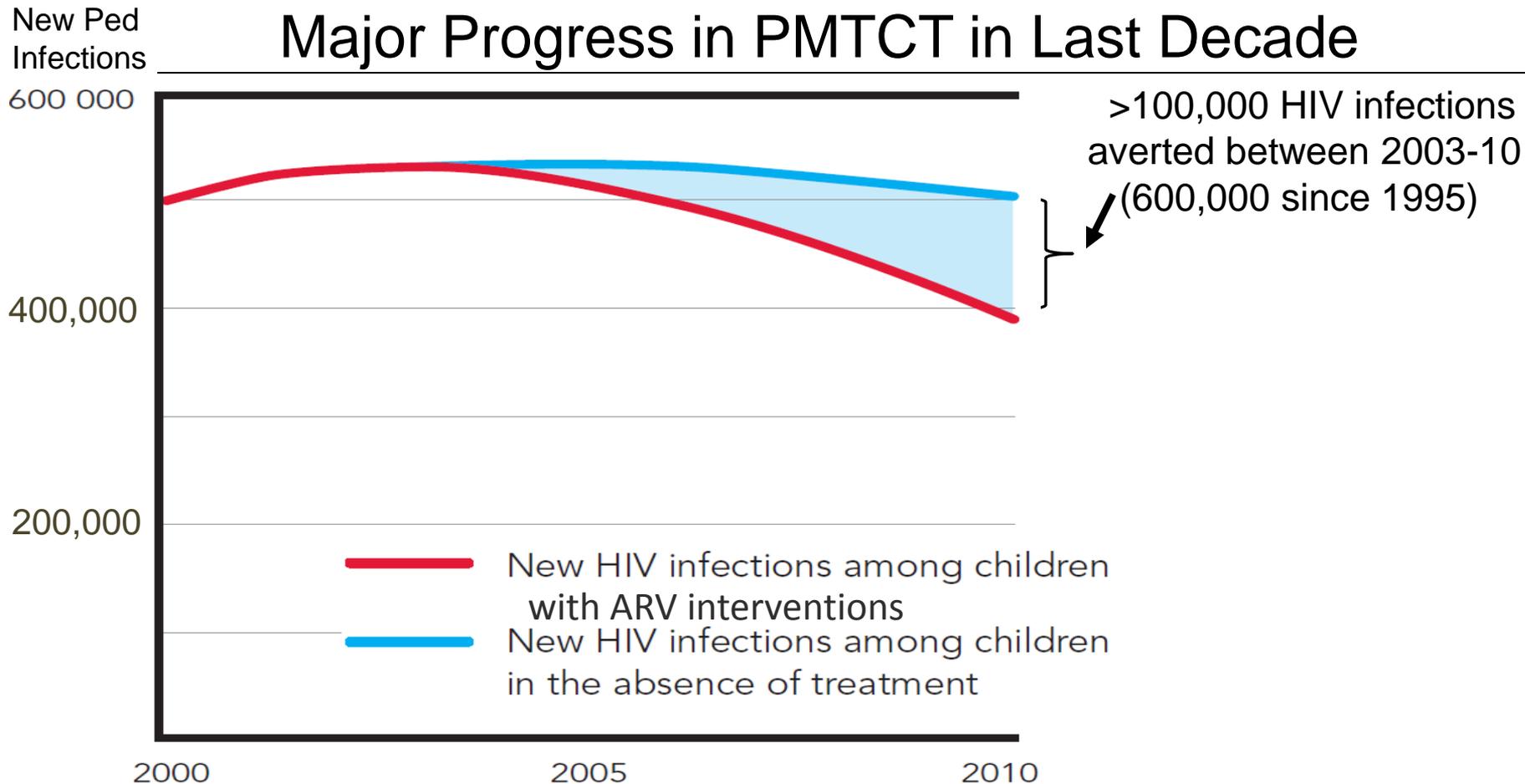
Launched by UNAIDS and PEPFAR; calls for exceptional global and national efforts.

Focuses on 22 countries with highest estimate of HIV-infected pregnant women.



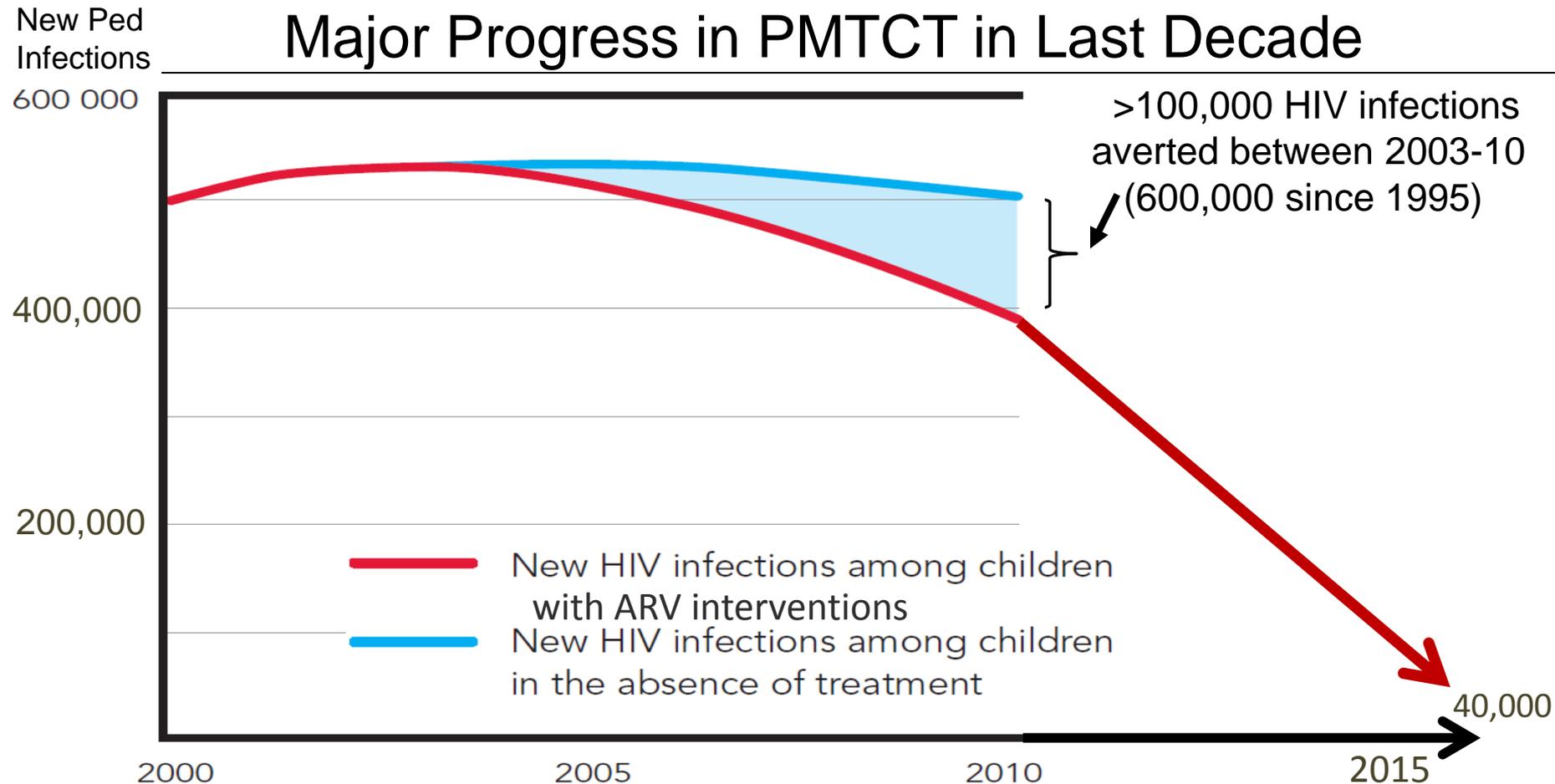
# Where are We in the Elimination Plan?

## Major Progress in PMTCT in Last Decade



# Where are We in the Elimination Plan?

## Major Progress in PMTCT in Last Decade



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## Major Progress in PMTCT in Last Decade

New Ped Infections

600 000

400,000

200,000

2000

2005

2010

2015

>100,000 HIV infections averted between 2003-10 (600,000 since 1995)

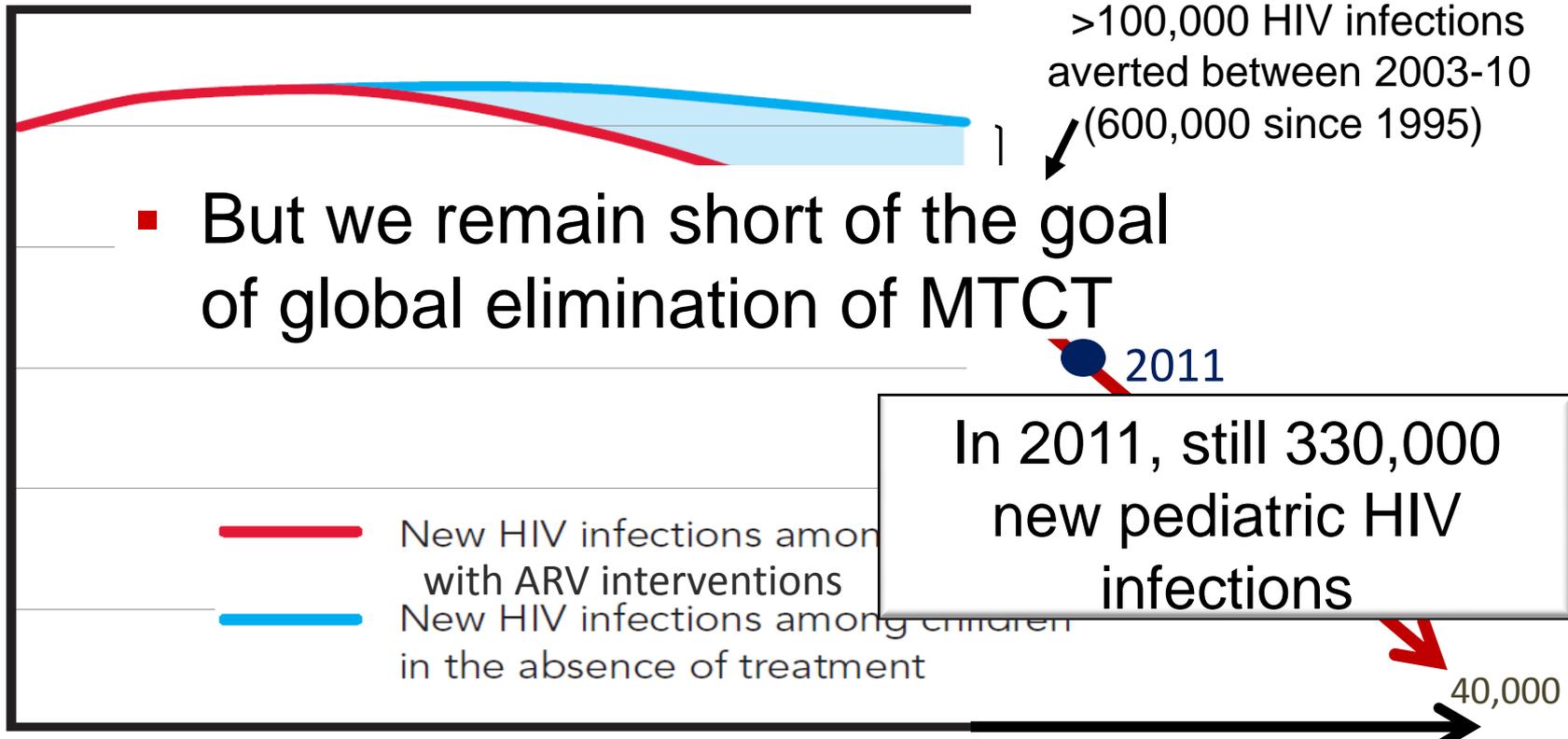
- But we remain short of the goal of global elimination of MTCT

— New HIV infections among adults with ARV interventions  
— New HIV infections among children in the absence of treatment

In 2011, still 330,000 new pediatric HIV infections

2011

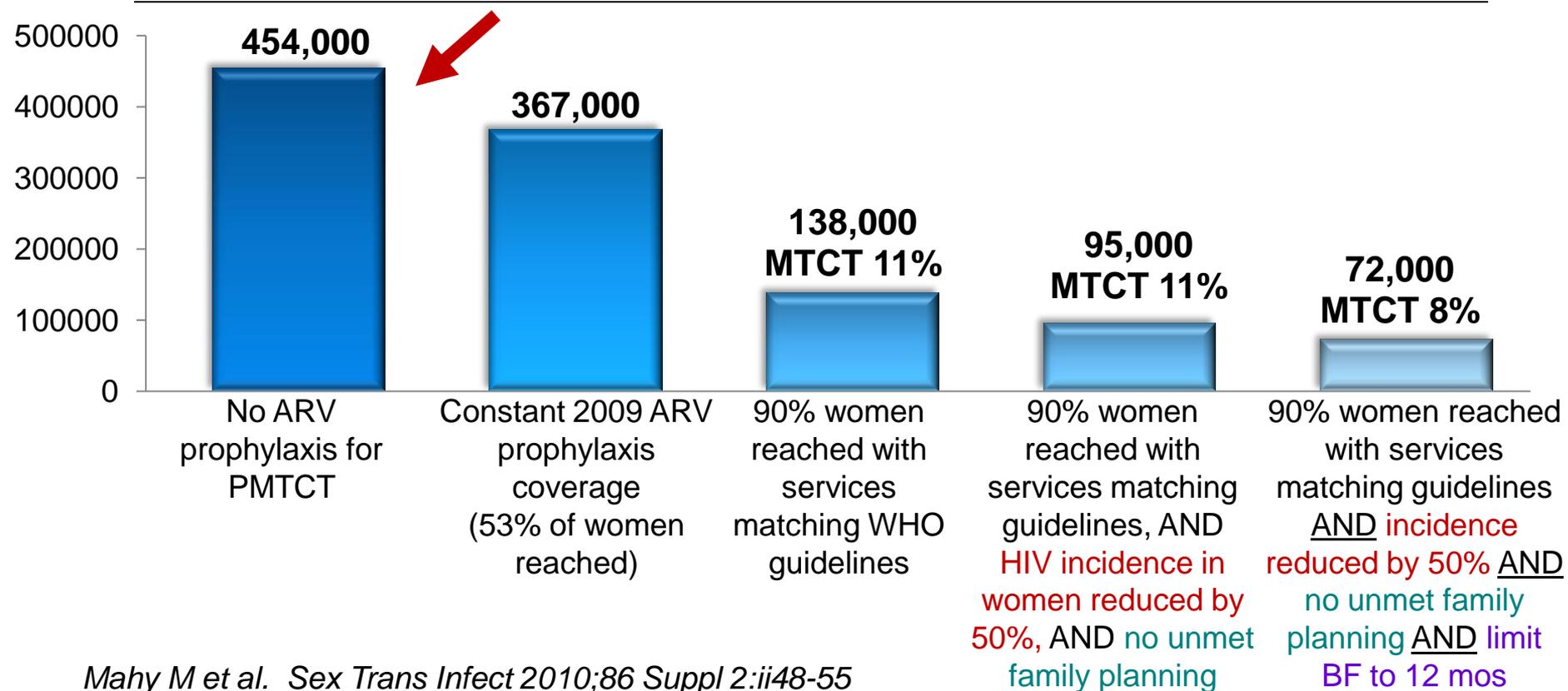
40,000



# Elimination of MTCT Requires More than Just ARVs:

New Perinatal HIV Infections, 25 Countries in the Year 2015:

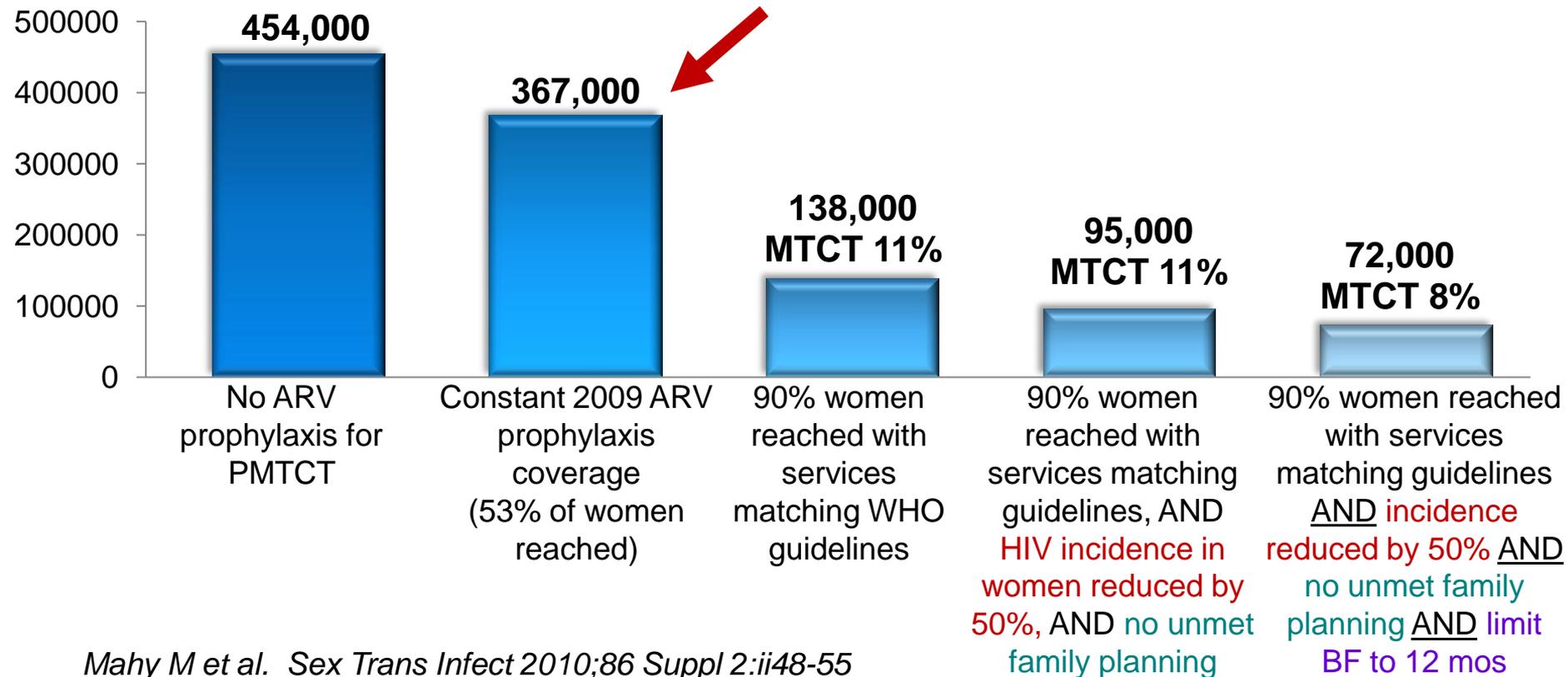
Virtual Elimination Goal <40,000 Perinatal Infections/Year and <5% MTCT



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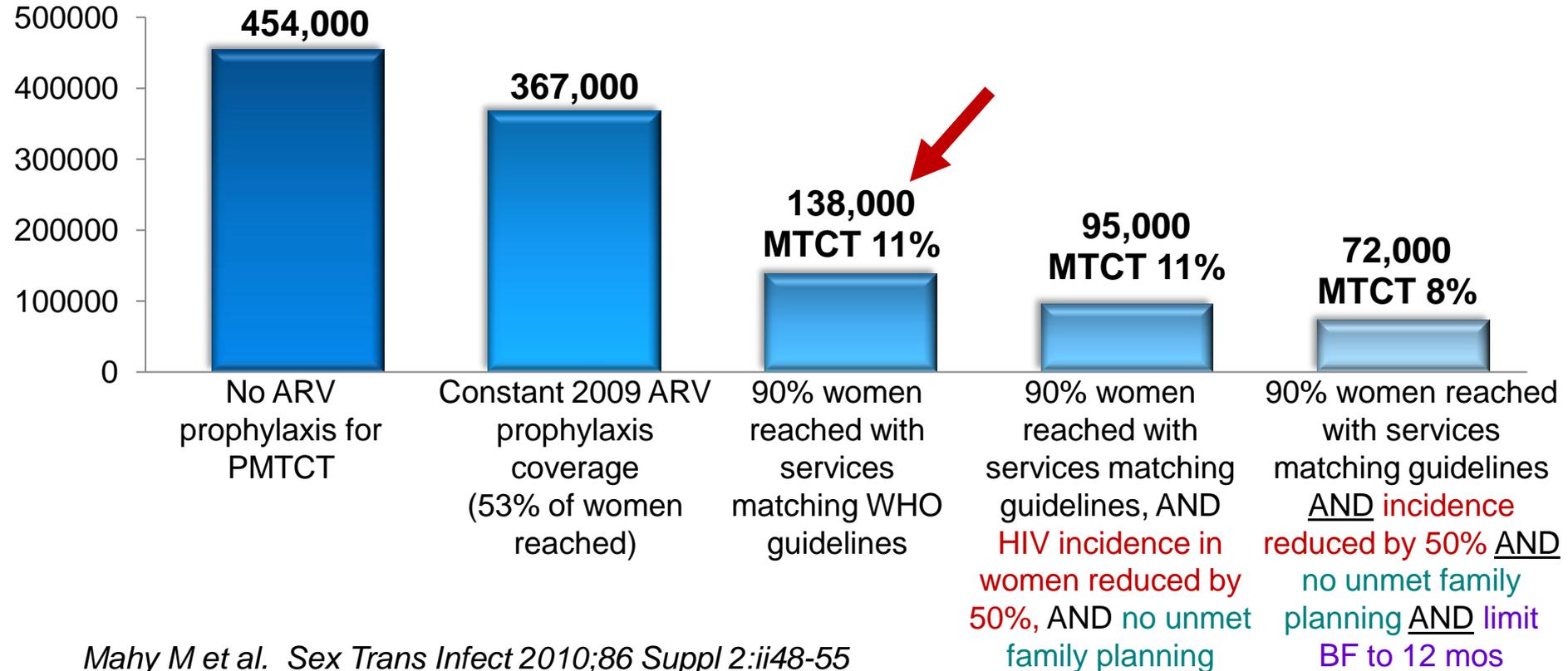
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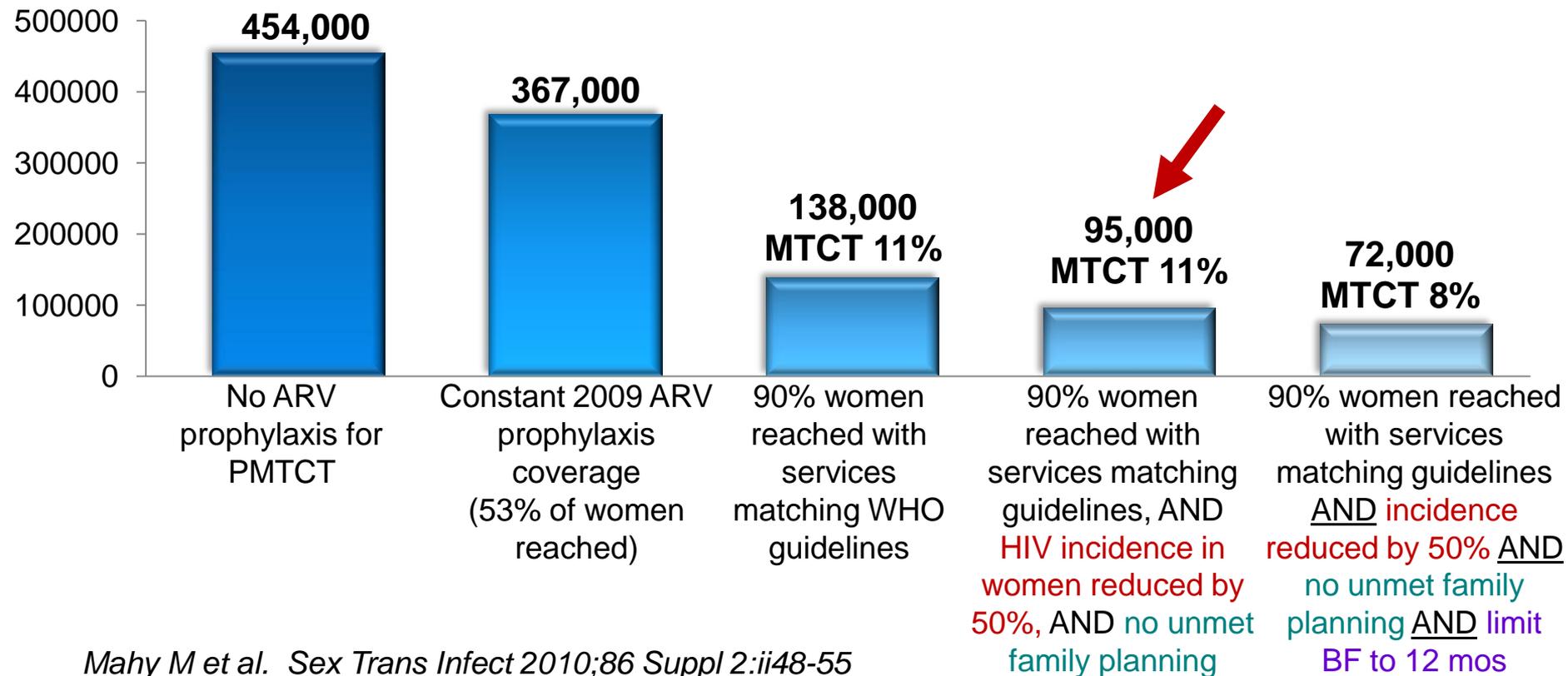
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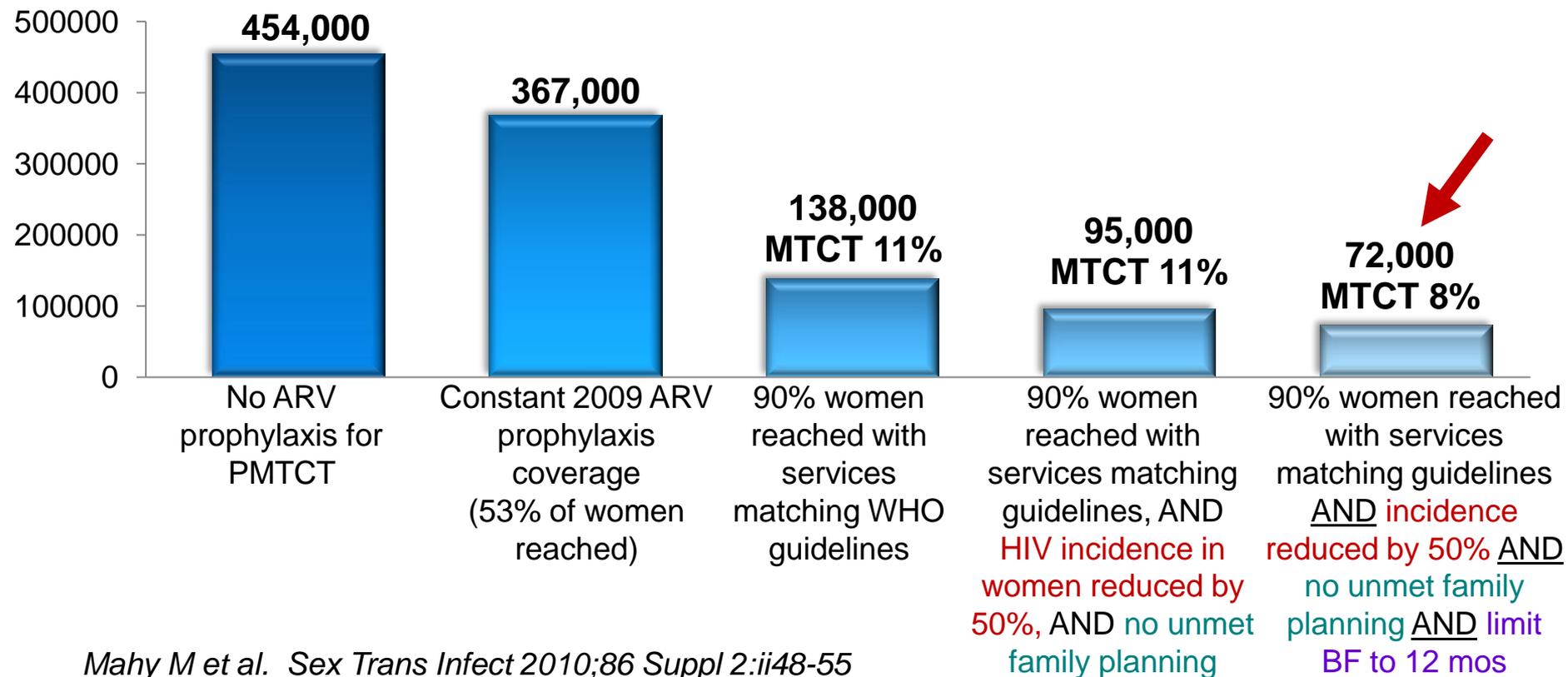
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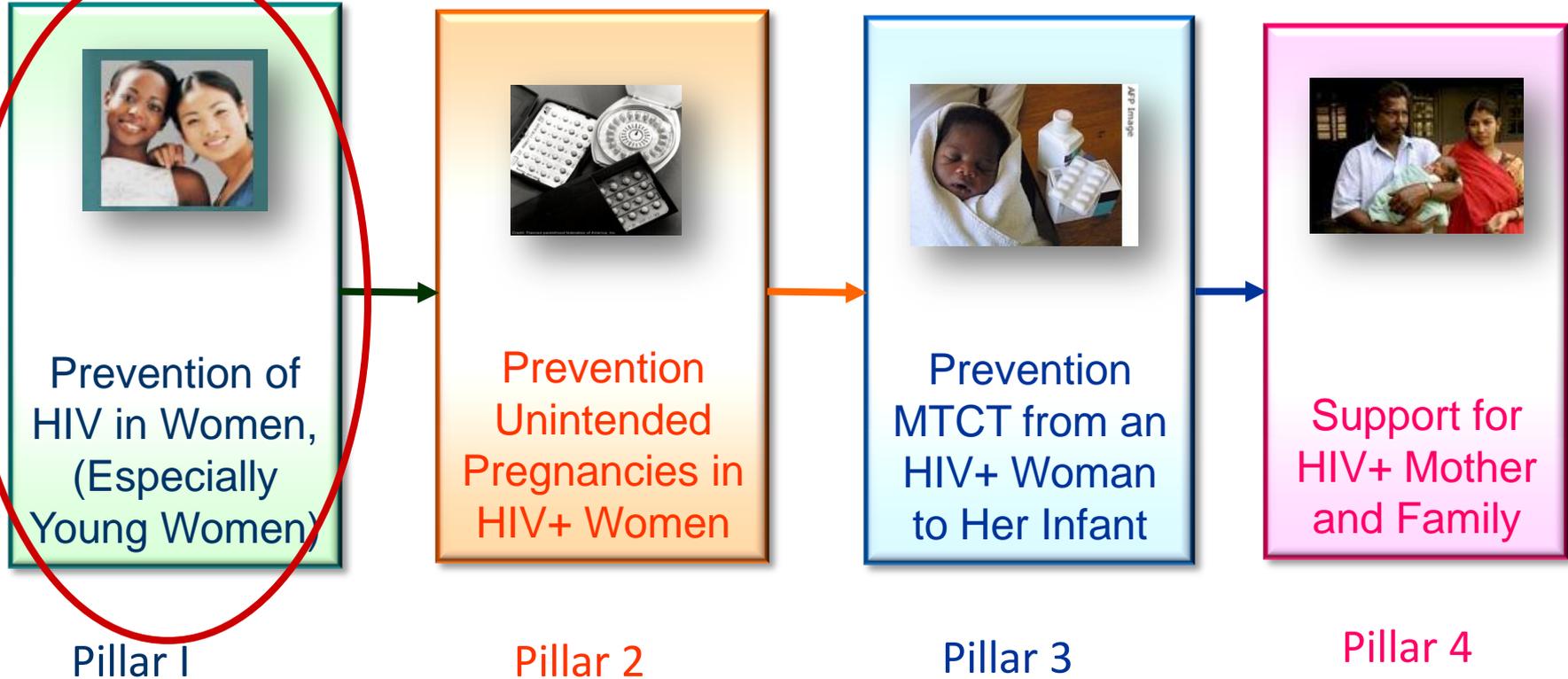
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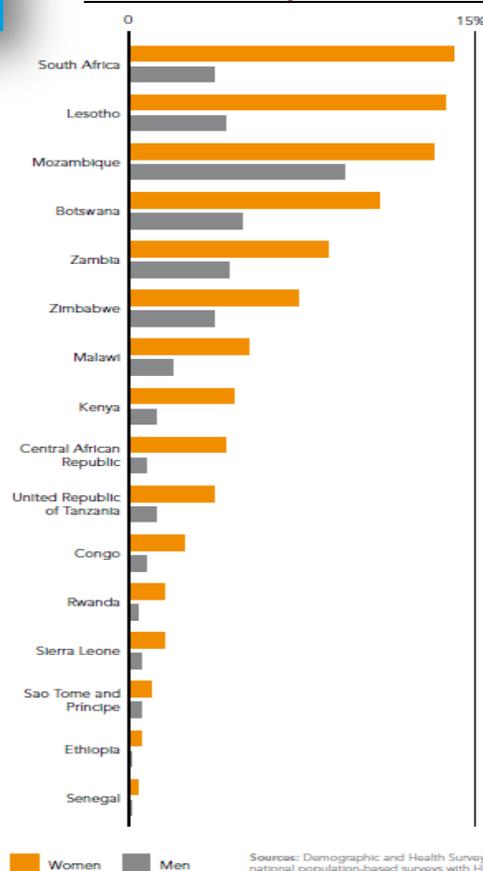


# PMTCT is More Than Just ARVs: Four Pillar Strategy for Prevention of MTCT

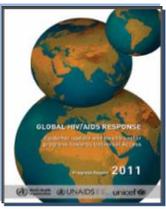
*Wilcher R et al. Sex Trans Inf 2008;84 (Suppl2):ii54-60*



## HIV Prevalence (%) Among People 15-24 Years Old, By Sex, Selected African Countries, 2008-2011



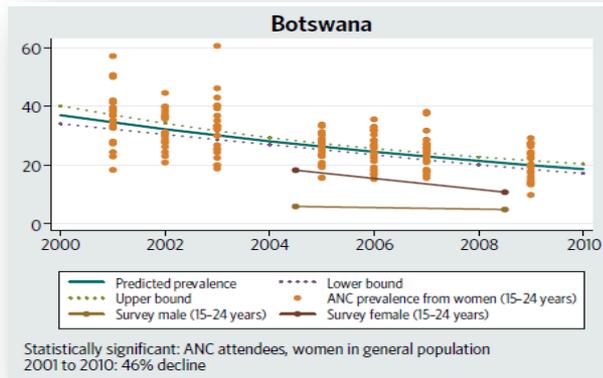
- Prevalence of HIV among young women in Sub-Saharan Africa is disproportionately higher than among young men.
- In 2010, in sub-Saharan Africa, 71% of people 15-24 years old living with HIV were women.



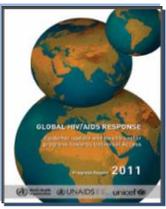
# Declining New HIV Infections in Young Women

## WHO 2011 Global HIV/AIDS Update

- Among 24 high prevalence countries, since 2000, there is average 31% decline in HIV in pregnant women in antenatal clinics.



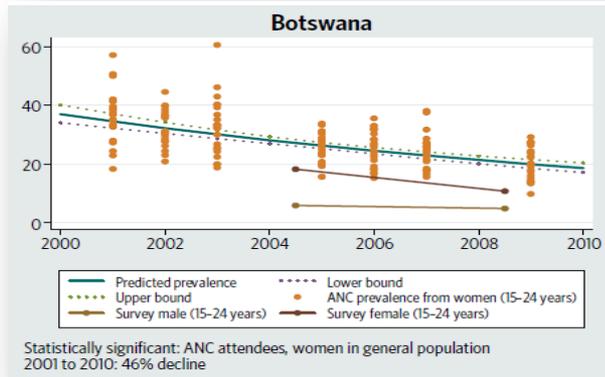
Botswana: 2001-2010, 46% decline



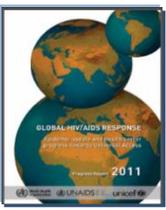
# Declining New HIV Infections in Young Women

*WHO 2011 Global HIV/AIDS Update*

- Among 24 high prevalence countries, since 2000, there is average 31% decline in HIV in pregnant women in antenatal clinics.
- The range, however, is wide – from >50% increase to >70% decline.
- 7/24 had a  $\geq 50\%$  reduction.



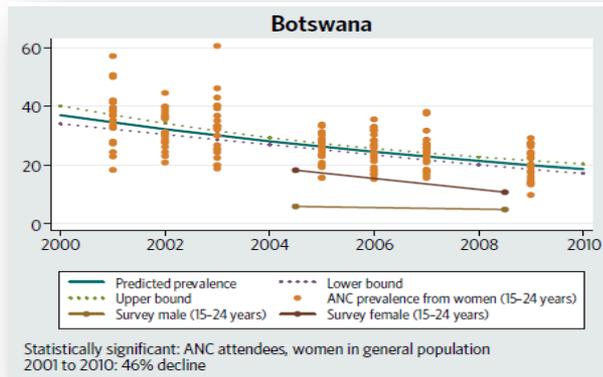
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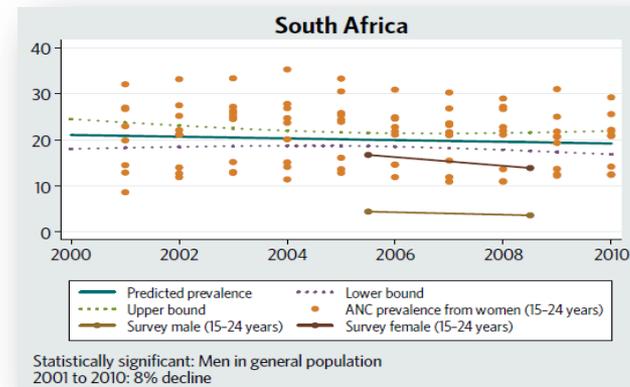
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- The range, however, is wide – from >50% increase to >70% decline.
- 7/24 had a  $\geq 50\%$  reduction.
- No decline in 5 others, including South Africa, with the largest HIV epidemic in the world.



Botswana: 2001-2010, 46% decline

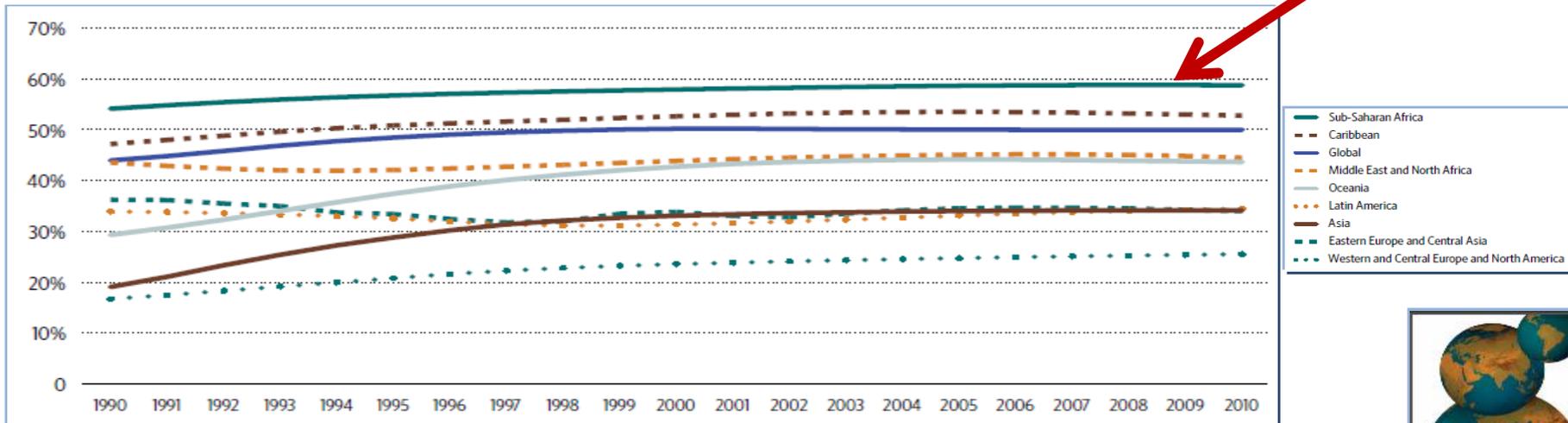


# Women Continue to Be Infected

- In countries most affected by HIV, women of childbearing age continue to constitute 50% or more of HIV-infected individuals in 2010.

## Trends in Women Living with HIV

Proportion of people age >15 years living with HIV who are female, 1990-2010



WHO 2011 Global HIV/AIDS Update



# High Incidence of HIV Reported During Pregnancy and Postpartum Period

- Risk of HIV acquisition may be increased during pregnancy; HIV incidence in pregnancy in low-resource countries ranges between 1.3-10.7%.

Country	Reference	Incidence Pregnancy per 100 Pt-Yrs
Uganda	Gray R et al. Lancet 2005;366:1182	2.3
Botswana	Lu L et al. 2009 CROI Abs.94LB	1.3 (0.5-3.1)
Zimbabwe, Uganda	Morrison CS et al. AIDS 2007;21:1027	1.6
South Africa	Rehle T et al. S Afr Med J 2007;97:194	5.2 (0-12.9)
South Africa	Moodley D et al. AIDS 2009;23:1255	10.7 (8.2-13.1)

# Acute Infection in Mother Associated with MTCT

- Risk of MTCT in infants of mothers with acute infection during pregnancy or lactation is increased ~3-fold over mothers with chronic HIV.

Author	Population	Acute/recent HIV infection	HIV Transmission to Infant
Moodley D (JID 2011; 203:1231-4)	1,396 HIV-uninfected women	3.4% seroconverted pregnancy or by 12 mo PP	<ul style="list-style-type: none"> <li>▪ <b>2.3-fold higher risk of MTCT</b> (Overall MTCT 20.5% acute vs 9.0% chronic HIV)</li> </ul>
Taha TE (AIDS 2011 May 21 epub)	2,561 HIV+ women (PP)	2.9% had recent infection	<ul style="list-style-type: none"> <li>▪ <b>2.5-fold higher risk in utero MTCT</b> In utero MTCT 17.8% acute vs 6.7% chronic HIV)</li> </ul>
Humphrey (BMJ 2010;341: c6580)	11,240 HIV-uninfected women	3.0% seroconverted postpartum	<ul style="list-style-type: none"> <li>▪ <b>2.8-fold higher risk postnatal MTCT</b> (Postnatal MTCT 23.6% acute vs 8.5% chronic HIV)</li> </ul>



# Zomba Malawi Cash Transfer Program: Financial Empowerment of School-Age Girls and Their Families

*Baird SJ, et al. Lancet 2012;379:1320-9*

## Intervention

The Zomba cash transfer programme took place between January, 2008, and December, 2009. In both years, transfers were made on a monthly basis for a total of ten transfers per year.

## Treatment groups

In the conditional group (baseline schoolgirls and baseline dropouts), each payment was received if the girl attended school for 80% of the days that school was in session during the previous month.

In the unconditional group (baseline schoolgirls only) payment was received if the girl attended the cash transfer points.

## Split

Cash transfers split between guardian and girl.

## Amounts

Household amount varied randomly (by use of computer-generated random numbers) by enumeration area, with monthly values of US\$4, \$6, \$8, or \$10. Girl amount varied randomly between individuals, with monthly values of \$1, \$2, \$3, \$4, or \$5, decided by drawing numbers from an envelope.

## Programme effects on untreated girls in treatment areas

Within treatment enumeration areas, a random subsample of baseline schoolgirls was not treated. The size of the subsample ranged from 0% to 100% per enumeration area.

- Community cluster-randomized trial in 1,706 girls 13-22 year old in Malawi; implemented for 2 school years.
- Randomized to cash payment to girl and parent (conditional school attendance in past month vs unconditional school attendance not required) vs control

# Cash Transfer Program and Effect on HIV and HSV-2

*Baird SJ, et al. Lancet 2012;379:1320-9*

18 Month Follow-Up Girls in School at Entry	Cash transfer	Control	Adjusted OR
HIV prevalence	7/490 (1%)	17/799 (3%)	0.36 (0.14-0.91)
HSV-2 prevalence	5/488 (<1%)	27/796 (3%)	0.24 (0.09-0.65)

- Also significantly lower rate older male partner or sex once per week
- Not powered for conditional vs unconditional but no significant difference
- Treatment effect did not vary by amount of cash

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18 Month Follow-Up <u>School Dropouts</u> at Entry	Cash transfer	Control	Adjusted OR
HIV prevalence	23/210 (10%)	17/207 (8%)	1.37 (0.72-2.61)
HSV-2 prevalence	17/211 (8%)	17/208 (8%)	1.03 (0.27-2.23)

# PMTCT is More Than Just ARVs: Four Pillar Strategy for Prevention of MTCT

*Wilcher R et al. Sex Trans Inf 2008;84 (Suppl2):ii54-60*



# Large Unmet Need for Family Planning in HIV-Infected Women in Resource-Limited Countries

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- There are an estimated 80 million unintended pregnancies annually among women.
- There is a high unmet need for family planning among women living with HIV
  - In studies in India, Rwanda, South Africa and Uganda, there are high rates of unintended pregnancies reported in women living with HIV, ranging from 43% - 70%.

*Suryavanshi N et al. AIDS Care 2008;20:1111-8*

*Kikuchi K, et al. Biosc Trends 2011;5:255-63*

*Wanyenze RK et al. J Int AIDS Soc 2011;14:35*

*Schwartz SR et al. PLoSOne 2012;7:e36039*

*Crede S et al. BMC Pub Health 2012;12:197*

# Unplanned Pregnancy in Women on ART, S.Africa

*Sheree R et al. PlosOne 2012;7:e36039*

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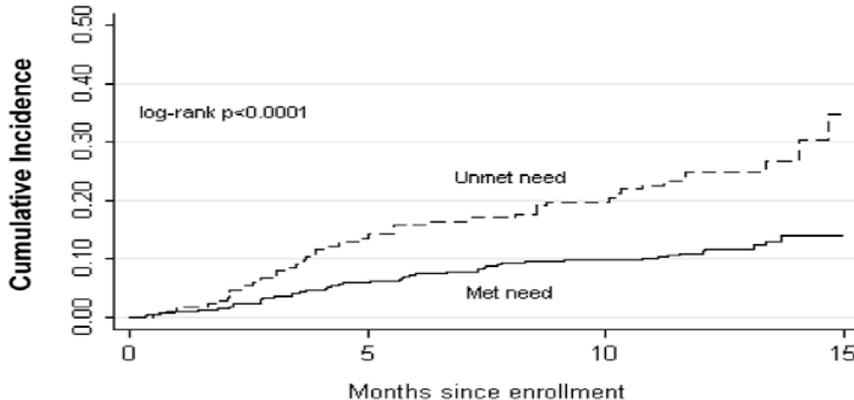
- Cohort of 850 non-pregnant women receiving ART in 4 public sector ART clinics in Johannesburg, S. Africa, 8/2009-3/2011.
- By 2 yrs post-ART, nearly 25% had  $\geq 1$  pregnancy; 35% by 3 yrs post-ART; of 170 pregnancies, 62% were unplanned.

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Incidence of unplanned pregnancy according to baseline need for contraception



- High pregnancy rates primarily driven by high unmet need for contraception.

# Childbearing Intentions of HIV-Infected Women of Reproductive Age in Soweto, S.Africa

*Kaida A et al. Am J Pub Health 2011;101:350-8*

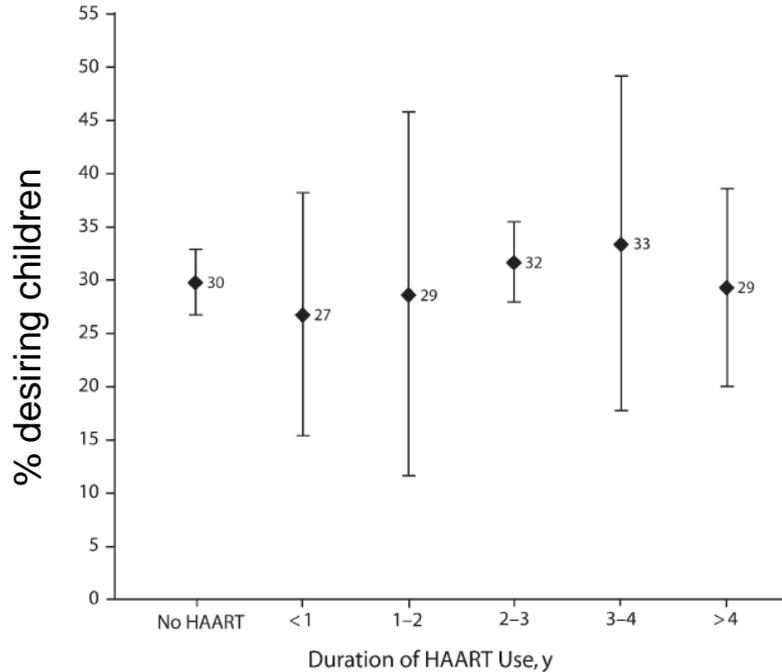
- Survey of 674 women aged 18-44 years attending Perinatal HIV Research Unit in 2007 regarding childbearing intentions.
- HIV+ women nearly 60% less likely to report childbearing intentions compared to HIV-negative women.

	Intends to have (more) children	Adjusted* OR
HIV uninfected (N=242)	69%	1.0
HIV-infected not on ART (N=215)	29%	0.35 (95% CI, 0.2-0.6)
HIV-infected, on ART (N=217)	31%	0.40 (95% CI, 0.2-0.7)

\*Adjusted for age, education, employment, income, current sexual relationship, number living children

# Childbearing Intentions of HIV-Infected Women of Reproductive Age in Soweto, S.Africa

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*Note.* Women (n=432) were aged 18 to 44 years and nonsterilized. Bars represent standard errors.

- There was also no association of duration of ART and reported childbearing intentions: only 27-33% of infected women reported wanting to have children.
- This means family planning is desired by 67-73% of infected women receiving ART.

# Integration of Family Planning into HIV Services

*Kaida A et al. PLoSOne 2010;5 (11):e13868*

- Perinatal HIV Research Unit Soweto (5-12/2007) – survey on contraceptive use in infected and uninfected women. Provides family planning in regular visits & contraception free.

	HIV-positive women			HIV-negative women (n= 214)	Overall (n= 563)	p-value <sup>§</sup>
	HAART users (n= 171)	HAART-naïve women (n= 178)	All HIV-positive women (n= 349)	n (%)	n (%)	
Contraceptive Prevalence	86%	82%	84%	69%	78%	<0.0001
(a) Mutually exclusive categories of type of contraceptive method used:						<0.0001
Dual protection (Hormonal/permanent method AND consistent condom use)	40%	24%	33%	14%	25%	
Hormonal/Permanent method only	18%	23%	20%	30%	24%	
Consistent condom use only	28%	35%	31%	25%	29%	
Not using any contraceptive method	14%	18%	16%	31%	22%	

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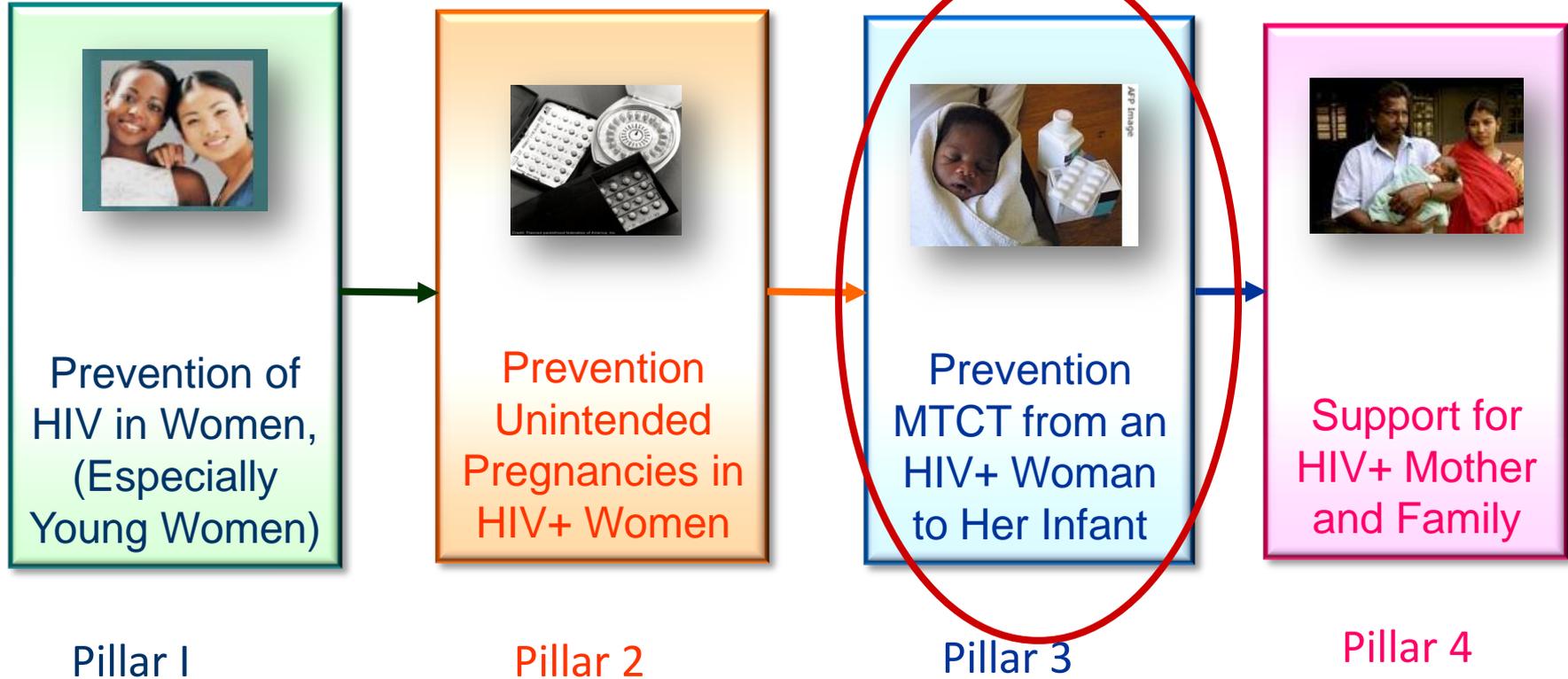
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- 78% reported contraceptive use; more frequent in HIV+ than HIV- women (84% HIV+, 69% HIV-).
- While contraceptive use was high, use of highly effective contraception was lower; 31% HIV+ relied on male condom only, which could result in unplanned pregnancy.

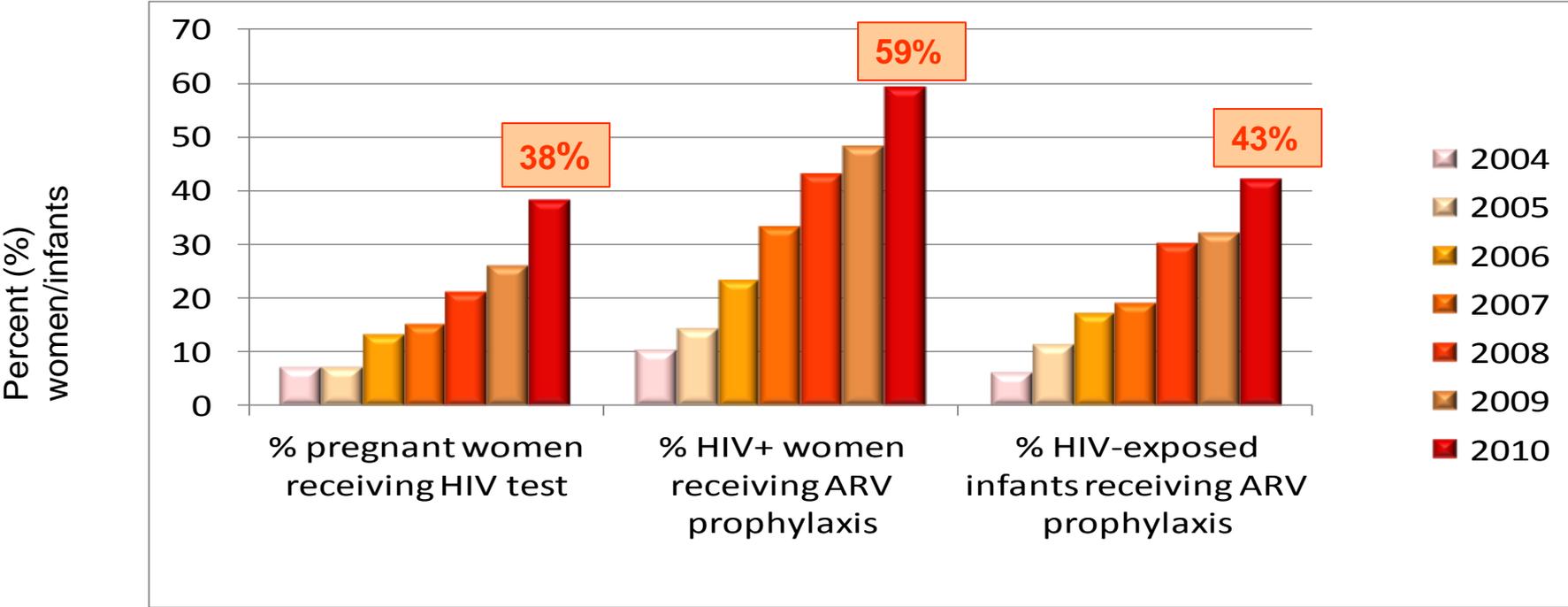
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# PMTCT in Low-Resource Countries Has Significantly Improved -- But is Still Below What is Needed



Adapted from WHO 2011 Global HIV/AIDS Update

# Meta-Analysis: Opt-Out vs Opt-In HIV Testing in Pregnancy

Wettstein C et al. AIDS 2012 Aug 21 (epub)

## Opt-Out HIV Testing

Author (year publication)

Manzi (2005)  
Homsy (2006)  
Zvandasara (2006)  
Wanyu (2007)  
Rutta (2008)  
Chama (2010)  
Chen (2010)  
Tsague (2010)  
Namukwaya (2011)

% Tested  
(95% CI)

Country

Study period

Author (year publication)	% Tested (95% CI)	Country	Study period
Manzi (2005)	94.6 (93.7-95.3)	Malawi	2002-2003
Homsy (2006)	96.0 (95.3-96.6)	Uganda	2004-2005
Zvandasara (2006)	88.9 (86.6-90.8)	Zimbabwe	2004-2005
Wanyu (2007)	99.1 (98.6-99.4)	Cameroon	2002-2005
Rutta (2008)	87.6 (87.0-88.2)	Tanzania	2002-2007
Chama (2010)	88.6 (87.8-89.4)	Nigeria	2007-2008
Chen (2010)	88.1 (86.8-89.3)	Botswana	2007-2008
Tsague (2010)	99.0 (98.9-99.0)	Rwanda	2006-2008
Namukwaya (2011)	99.7 (99.7-99.8)	Uganda	2007-2009

Overall

93.7%, 95% CI 92.4-95.0%

0 20 40 60 80 100  
Percentage of pregnant women tested for HIV at ANC clinics

## Opt-In HIV Testing

Author (year publication)

Ekouevi (2004)  
Stringer (2005)  
Chama (2007)  
Peltzer (2008)  
Shetty (2008)  
Stinson (2010)  
Balcha (2011)

% Tested  
(95% CI)

Country

Study period

Author (year publication)	% Tested (95% CI)	Country	Study period
Ekouevi (2004)	89.1 (87.8-90.3)	Côte d'Ivoire	2002
Stringer (2005)	58.6 (57.6-59.6)	Zambia	2003
Chama (2007)	16.6 (15.6-17.7)	Nigeria	2002-2004
Peltzer (2008)	49.4 (46.9-51.9)	South Africa	2005-2006
Shetty (2008)	54.5 (53.8-55.2)	Zimbabwe	2002-2004
Stinson (2010)	88.1 (87.6-88.6)	South Africa	2005
Balcha (2011)	46.5 (46.3-46.8)	Ethiopia	2007-2008

Overall

57.6%, 95% CI 40.0-75.1%

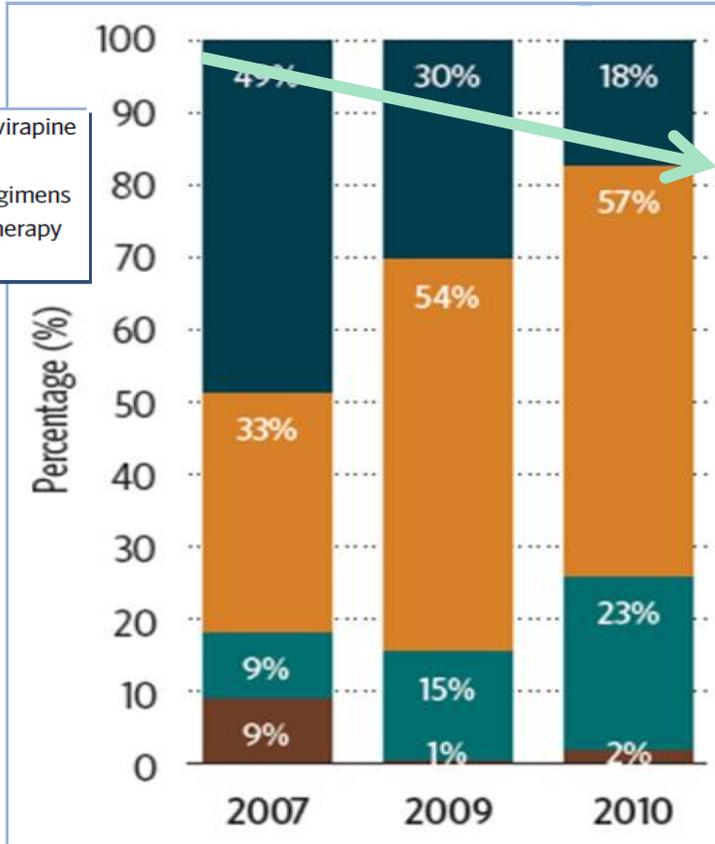
0 20 40 60 80 100  
Percentage of pregnant women tested for HIV at ANC clinics

- In 9 studies with sites with provider-initiated (opt-out) testing, combined estimate of women tested for HIV was 93.7%

- In 7 studies with sites with opt-in testing, combined estimate of women tested for HIV was 57.6%

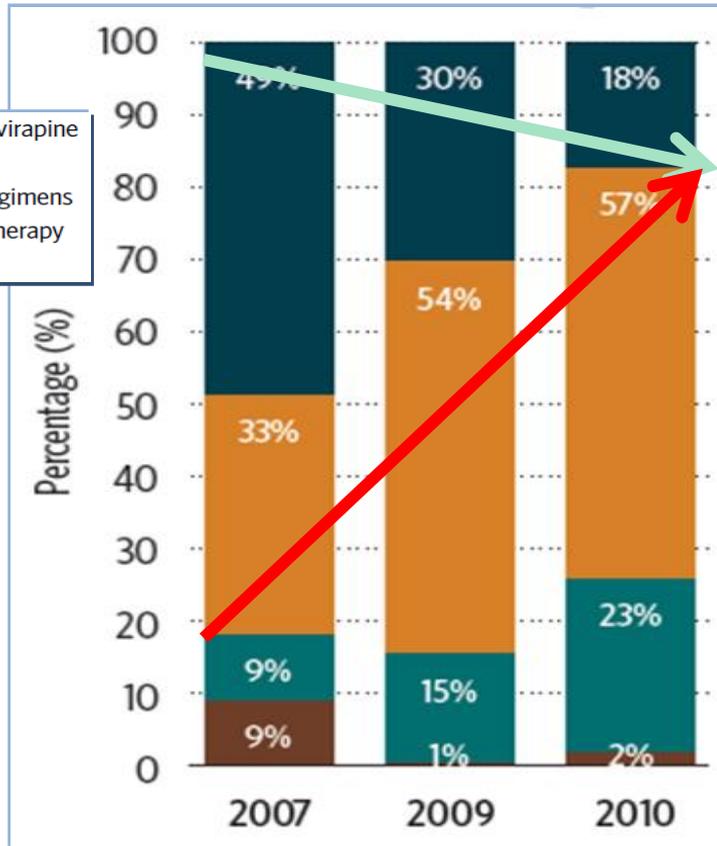
Predictors testing (6 studies): cART provided at ANC; accompanied by male partner

# Use of More Effective ARV Prophylaxis for PMTCT Has Significantly Increased



sdNVP  
49% 2007 to 18% 2010

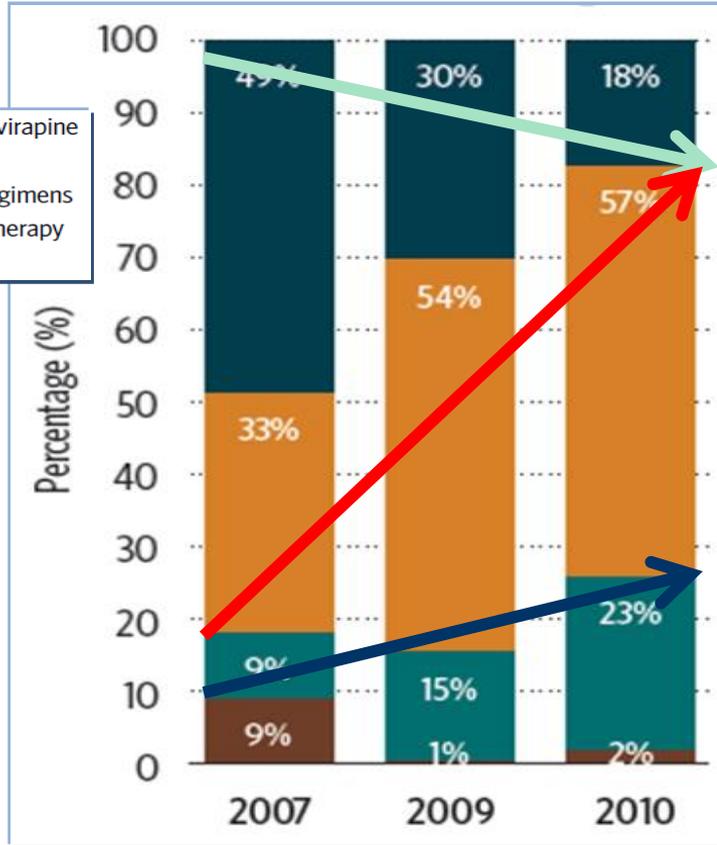
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Multi-drug  
33% 2007 to 57% 2010

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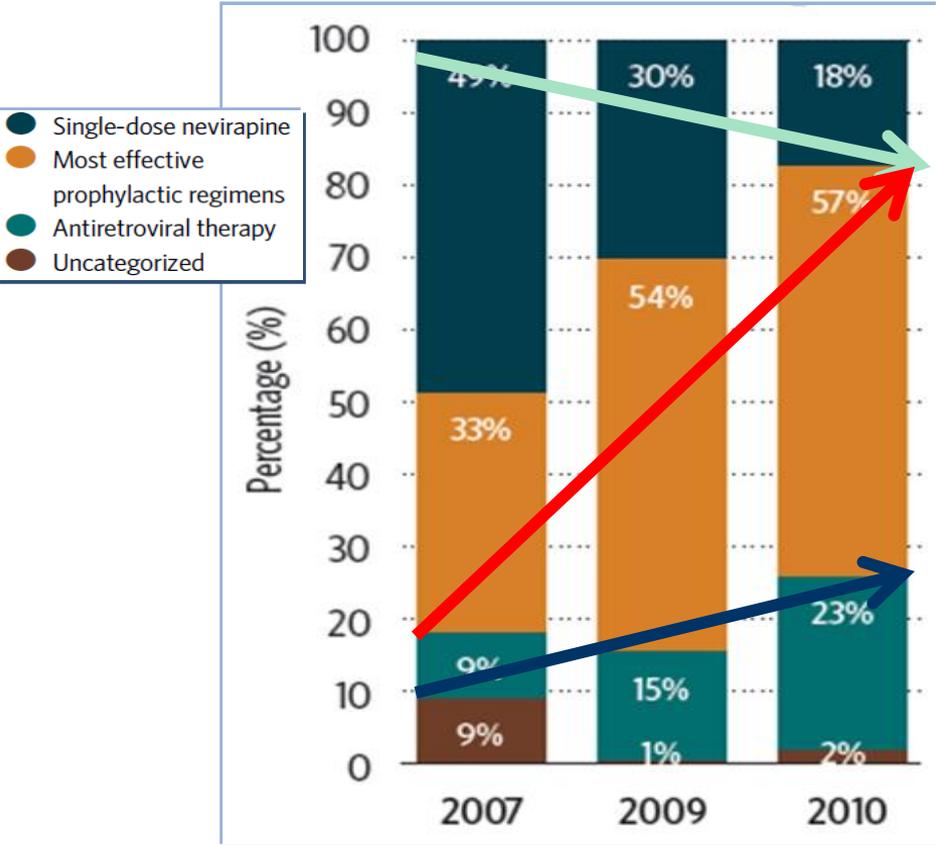


sdNVP  
49% 2007 to 18% 2010

Multi-drug  
33% 2007 to 57% 2010

ART  
9% 2007 to 23% 2010

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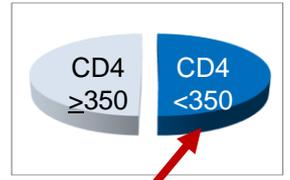
sdNVP  
49% 2007 to 18% 2010

Multi-drug  
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ART  
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But  
>50% Actually  
Require ART

3,736 HIV+ pregnant women  
13 MTCT-Plus Countries  
Carter R. JAMA 2010

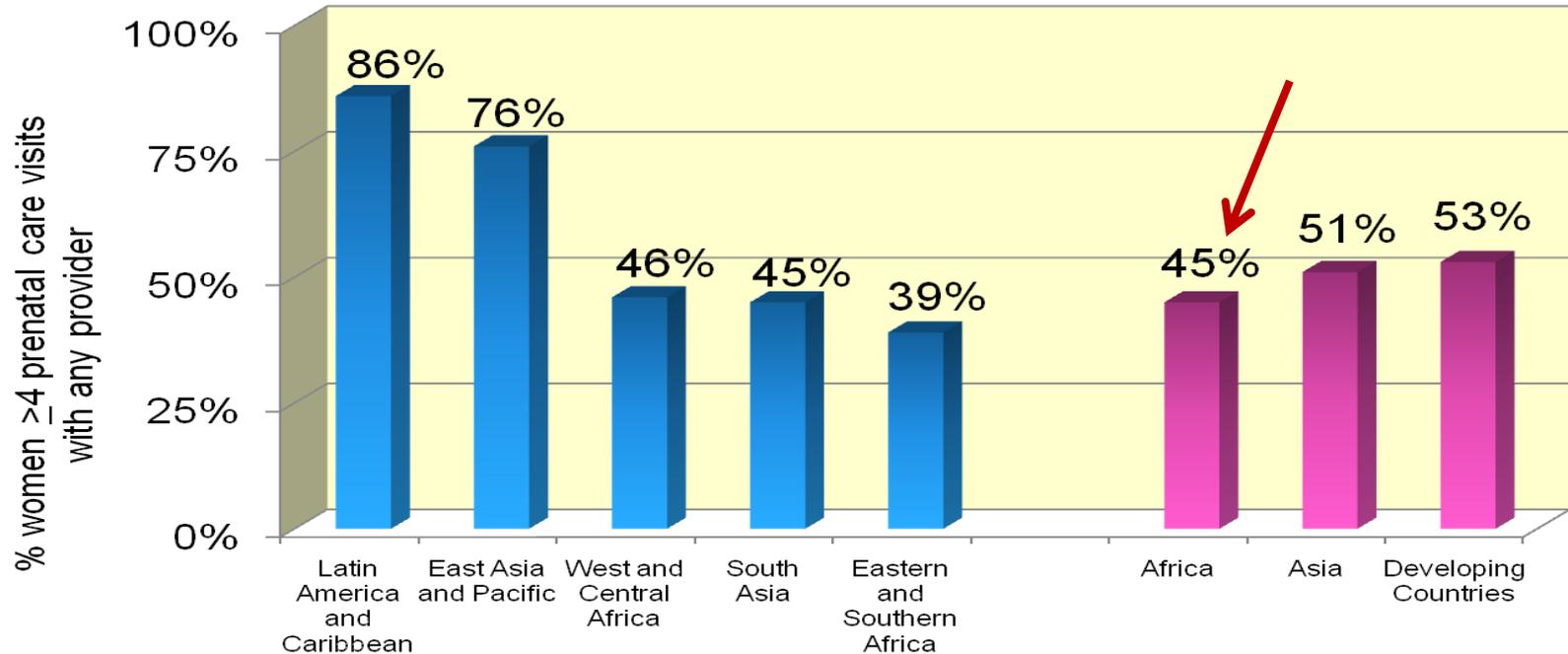


50.3%  
CD4 < 350

# Late Entry into Prenatal Care Common in Developing Countries

Only 53% of Women Receive Recommended 4 Antenatal Visits

UNICEF: [http://www.childinfo.org/antenatal\\_care.html](http://www.childinfo.org/antenatal_care.html)



# For Maximal Efficacy, Early ARV Initiation Needed

## ARV Duration in Pregnancy and MTCT: Johannesburg, S. Africa

*Hoffman R et al. JAIDS 2010;54:35-41*

Group	(873 pregnant women with advanced HIV infection)	% MTCT
Overall group women <u>all on HAART</u> (N=873)		4.9%
(no sig. difference NVP vs LPV/r vs EFV regimen)		
On HAART when became pregnant		0.7%
(N=143, median duration 93.4 weeks by delivery)		
Started HAART during pregnancy		5.7%
(N=730, median duration 10.7 weeks by delivery)		
Duration of HAART during pregnancy:		
<4 weeks (N=151)		9.3%
4-16 weeks (N=422)		5.5%
16-32 weeks (N=157)		3.5%



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 p= 0.01

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*Hoffman R et al. JAIDS 2010;54:35-41*

Group	(873 pregnant women with advanced HIV infection)	% MTCT
Overall group women <u>all on HAART</u> (N=873)		4.9%
(no sig. difference NVP vs LPV/r vs EFV regimen)		
On HAART when became pregnant		0.7%
(N=143, median duration 93.4 weeks by delivery)		
Started HAART during pregnancy		5.7%
(N=730, median duration 10.7 weeks by delivery)		
Duration of HAART during pregnancy:		
<4 weeks (N=151)		9.3%
4-16 weeks (N=422)		5.5%
16-32 weeks (N=157)		3.5%

In women starting HAART during pregnancy, each additional week of HAART reduced odds of transmission by 8% (adjusted OR 0.92, 95% CI 0.87-0.99)

# Need to Address Operational Issues, Not Just ARV, to Eliminate Pediatric HIV

PMTCT Cascade with Universal WHO Guidelines and Meeting PEPFAR Goals

1000 HIV+mothers

Attend ANC: 80%



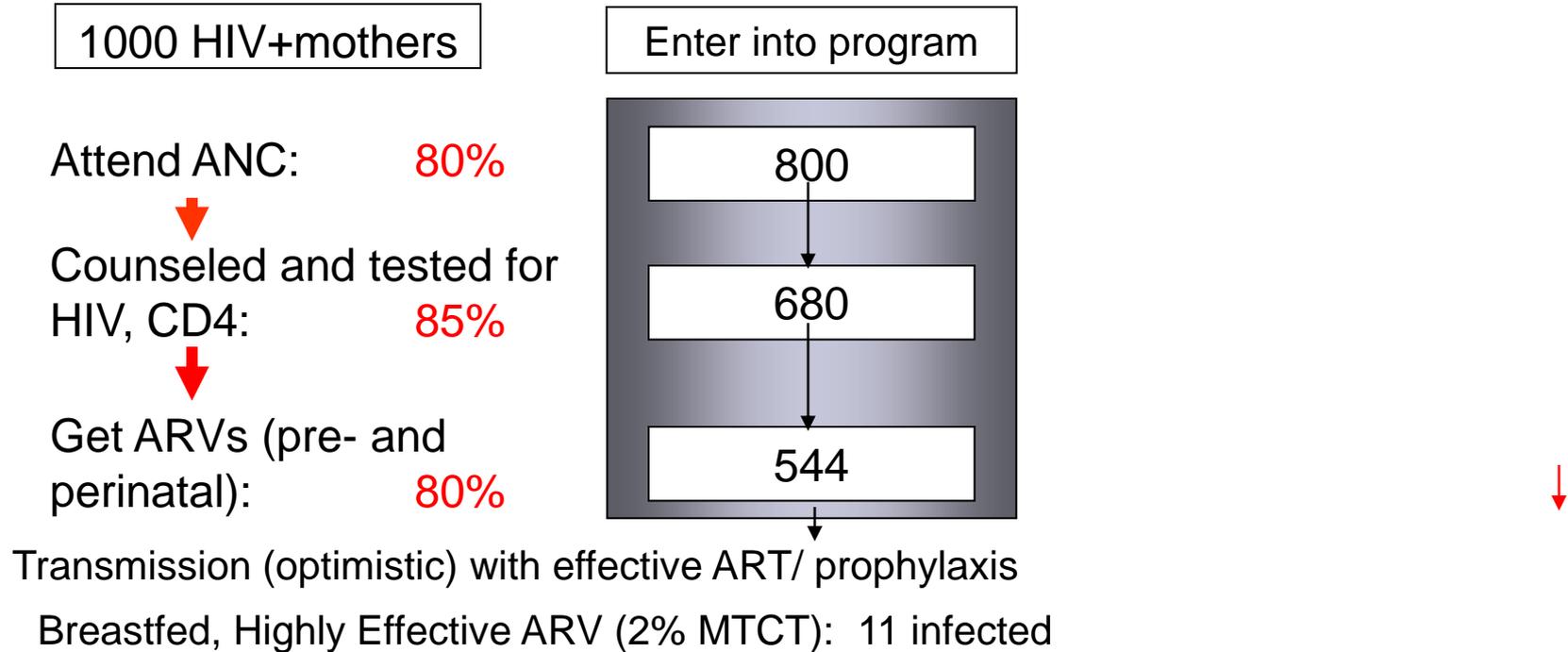
Counseled and tested for  
HIV, CD4: 85%



Get ARVs (pre- and  
perinatal): 80%

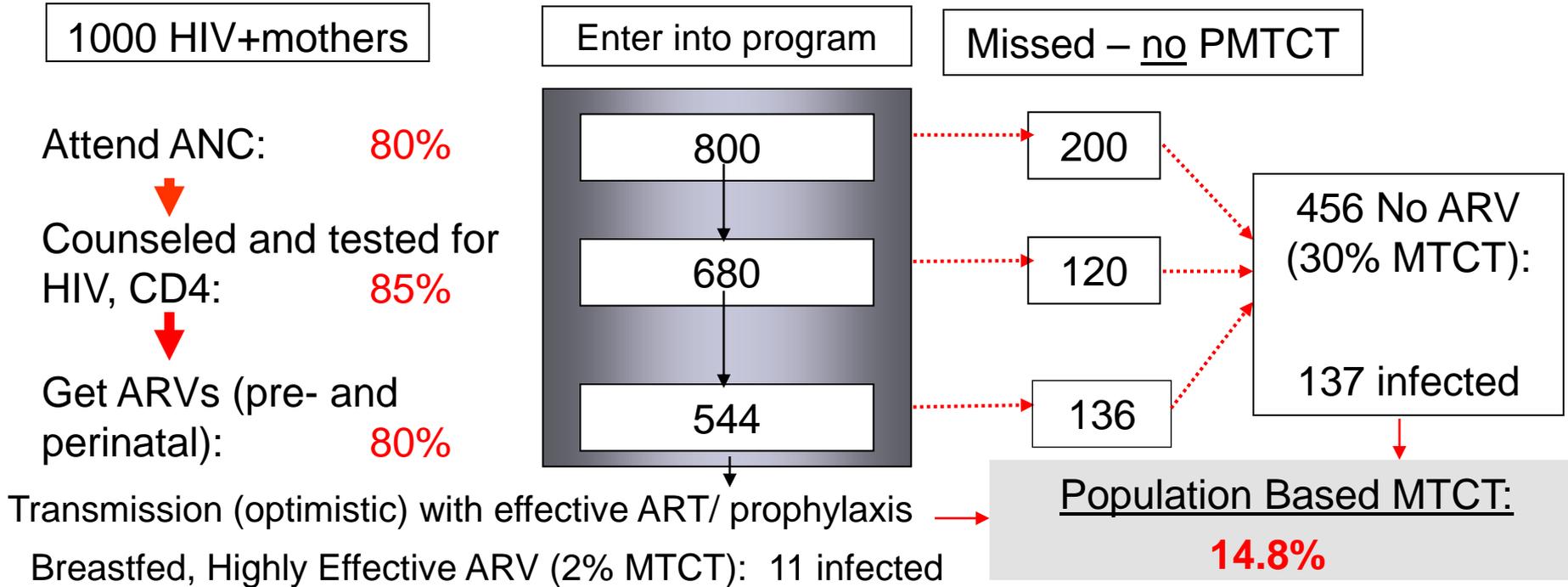
# Need to Address Operational Issues, Not Just ARV, to Eliminate Pediatric HIV

## PMTCT Cascade with Universal WHO Guidelines and Meeting PEPFAR Goals



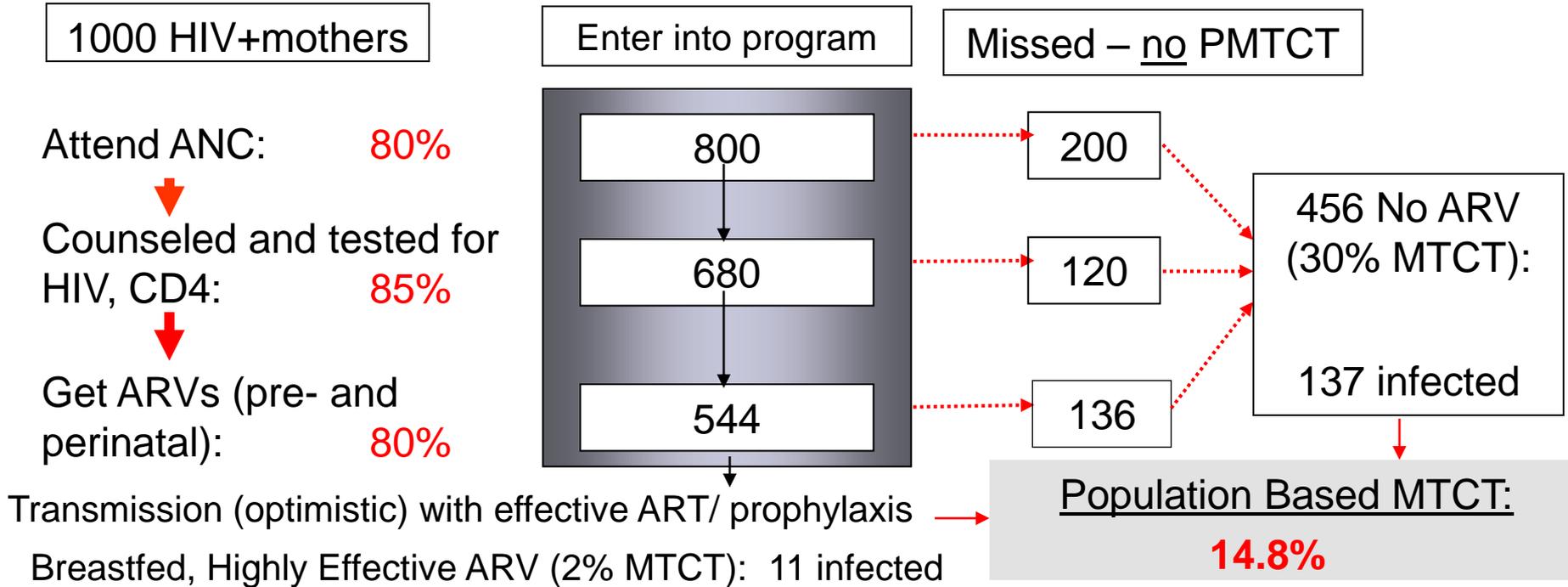
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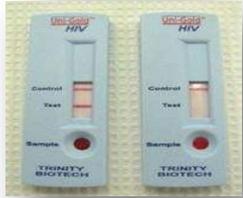
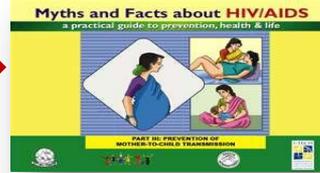
**2 million HIV+ pregnant women/yr = 296,000 infected infants born annually**

# What is Needed to Prevent MTCT: The PMTCT Cascade



What Does This Really Entail?

# What is Needed to Prevent MTCT: The PMTCT Cascade

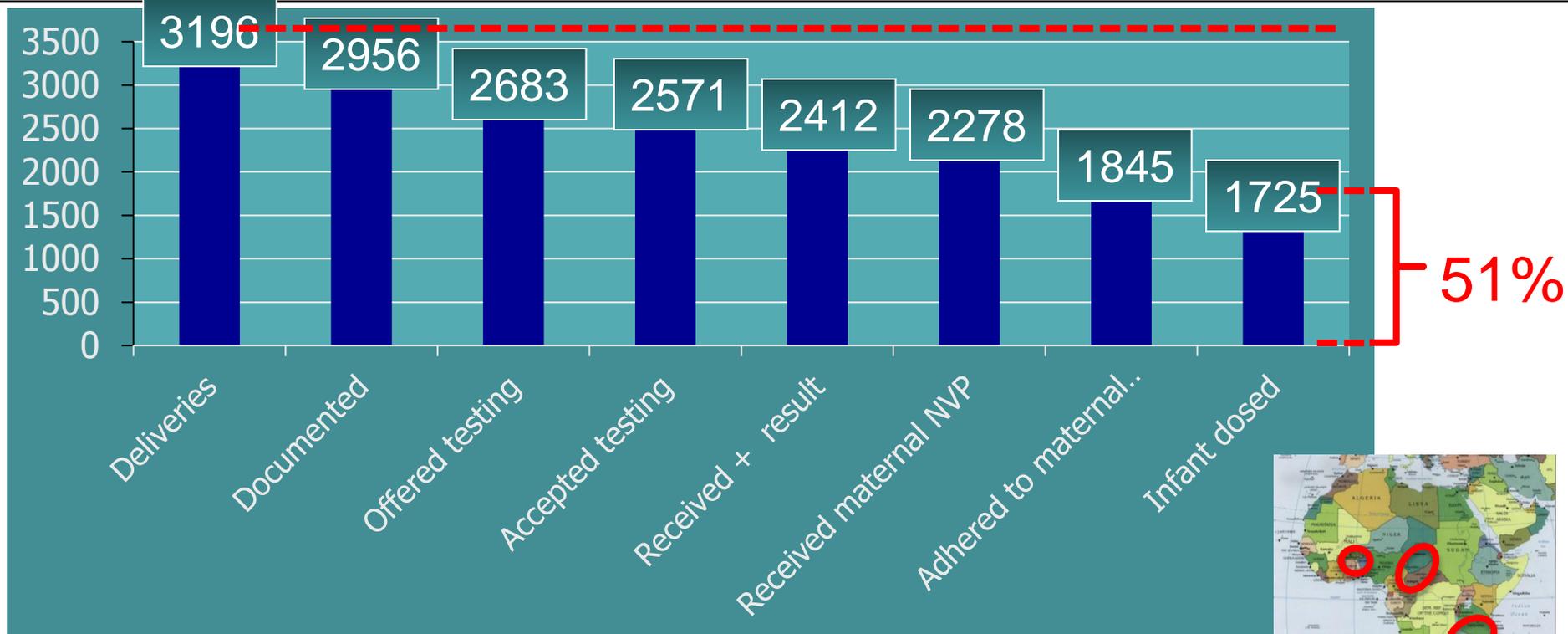


# What is Needed to Prevent MTCT: The PMTCT Cascade (continued)



# PMTCT Coverage – 27,893 Live Births in 4 High-Prevalence African Countries (PEARL Study)

*Stringer EM et al. JAMA 2010;304:293-302*

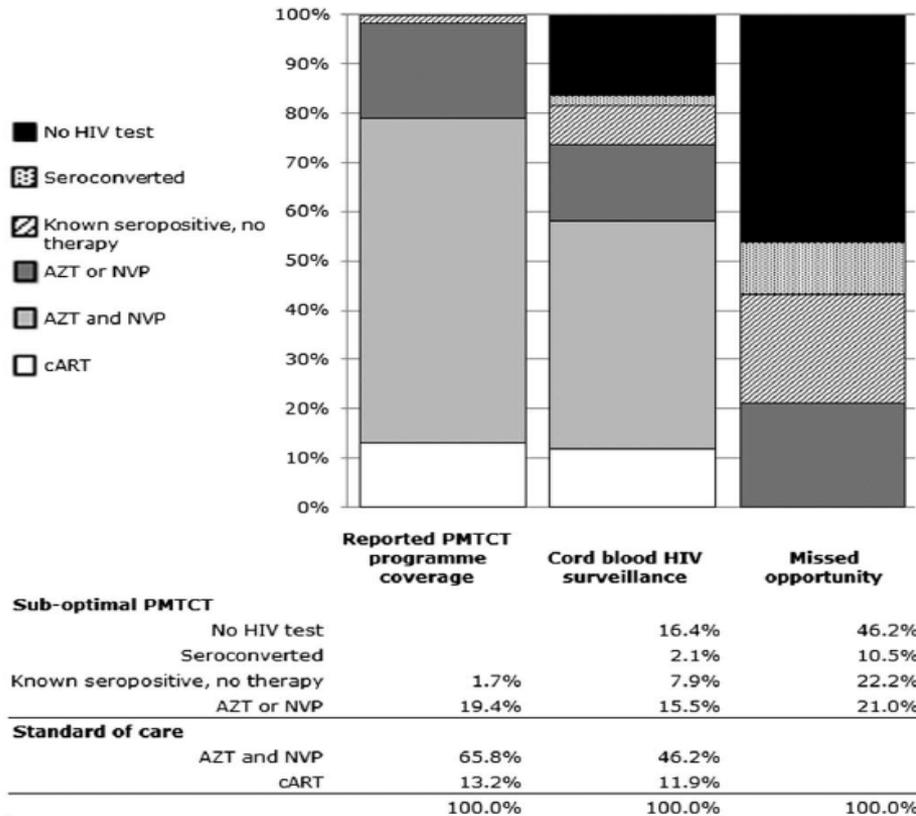


PMTCT cascade for HIV-infected women



# Missed Opportunities in PMTCT, Western Cape, S. Africa

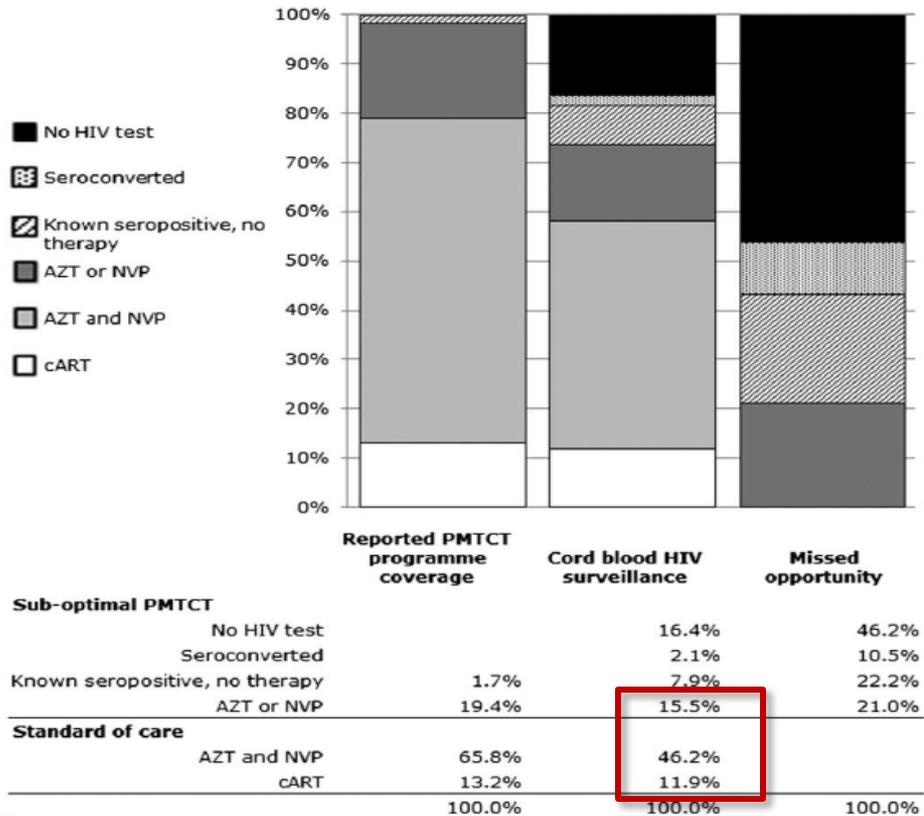
*Stinson JAIDS 2012;60:199-203*



- 3,034 cord blood tested for HIV; 507 (16.7%) HIV+
- 470 (93%) of HIV+ cord blood tested for ARVs

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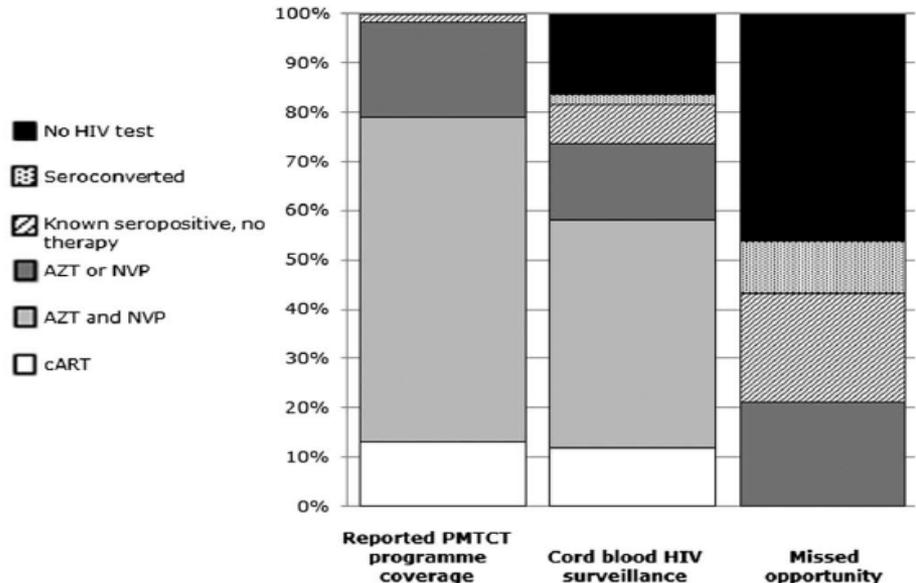
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## Sub-optimal PMTCT

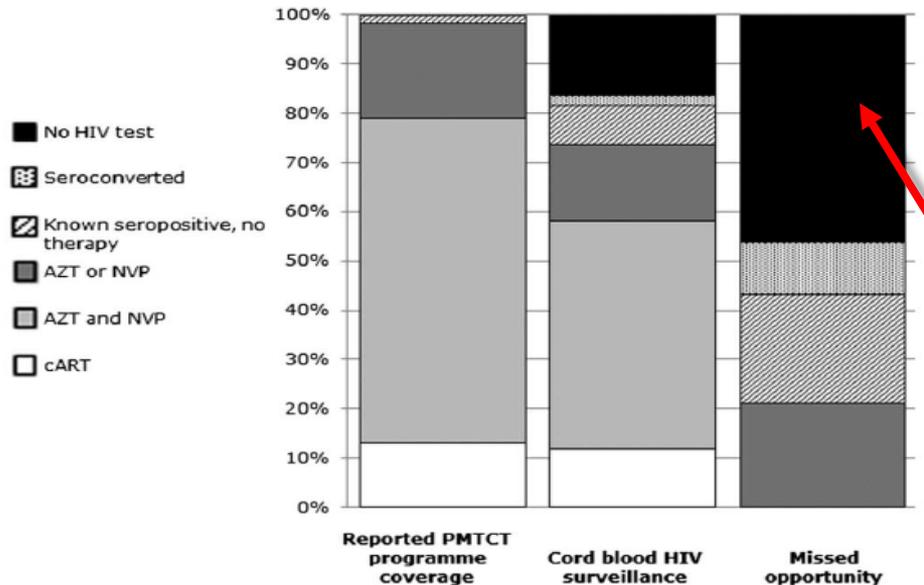
	Reported PMTCT programme coverage	Cord blood HIV surveillance	Missed opportunity
No HIV test		16.4%	46.2%
Seroconverted		2.1%	10.5%
Known seropositive, no therapy	1.7%	7.9%	22.2%
AZT or NVP	19.4%	15.5%	21.0%

## Standard of care

AZT and NVP	65.8%	46.2%	
cART	13.2%	11.9%	
	100.0%	100.0%	100.0%

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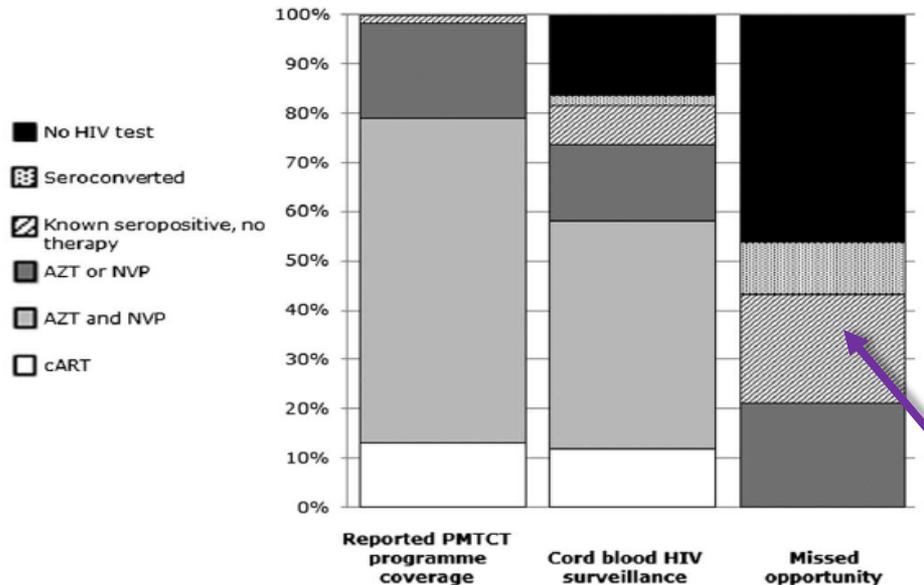
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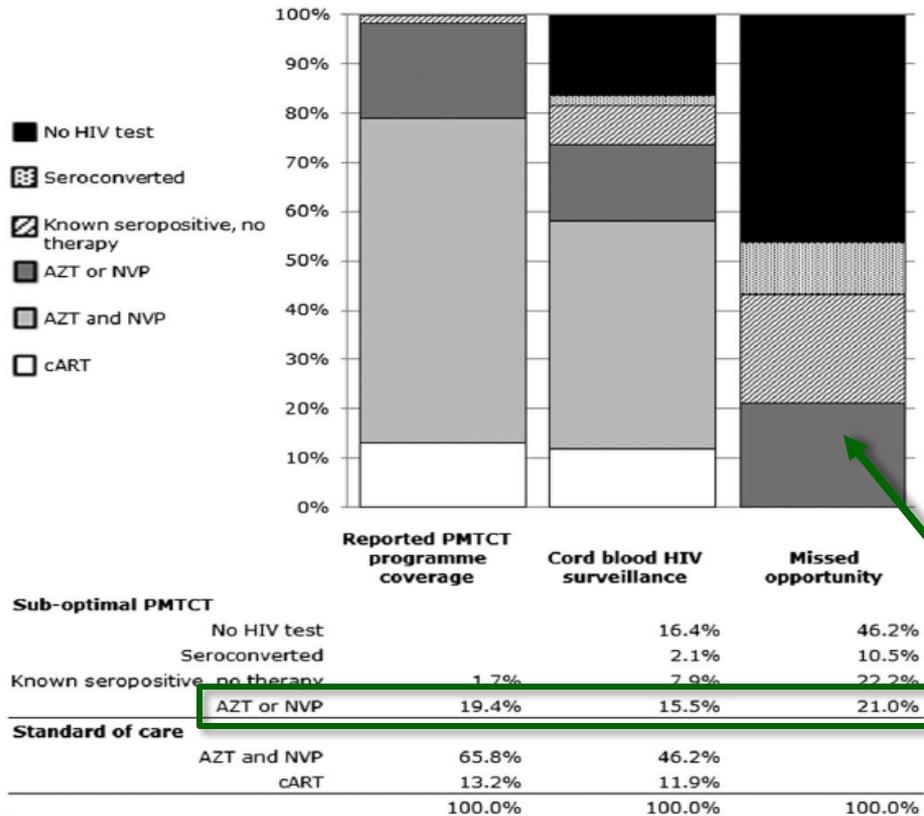
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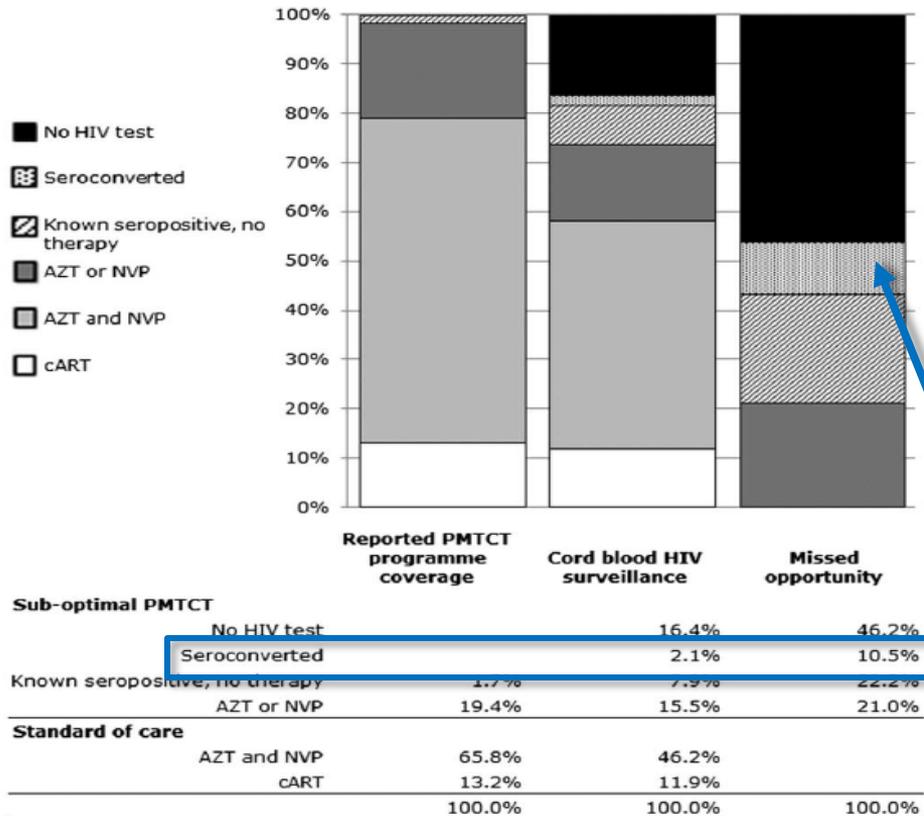
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Known HIV+ but no ARV 22.2%

Suboptimal ARV, 21%

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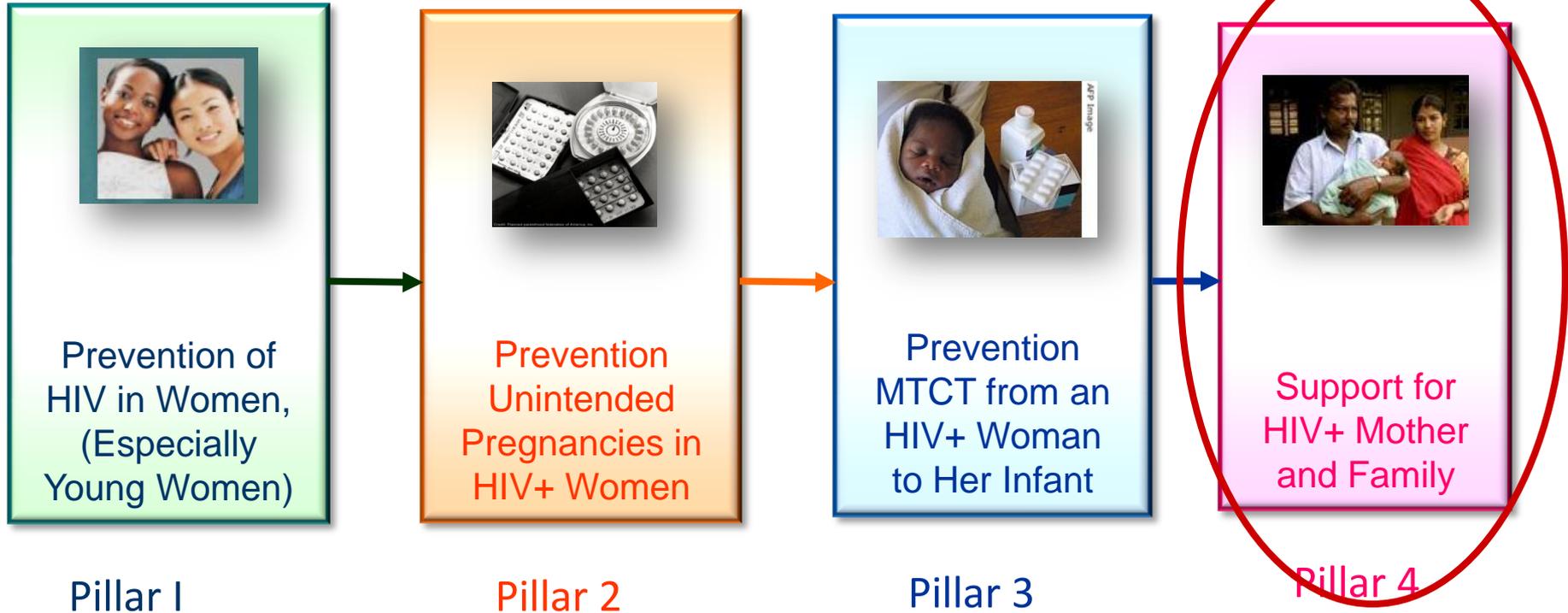
Known HIV+ but no ARV 22.2%

Suboptimal ARV, 21%

Acute infection, 10.5%

# PMTCT is More Than Just ARVs: Four Pillar Strategy for Prevention of MTCT

*Wilcher R et al. Sex Trans Inf 2008;84 (Suppl2):ii54-60*



# PMTCT Doesn't End at Delivery

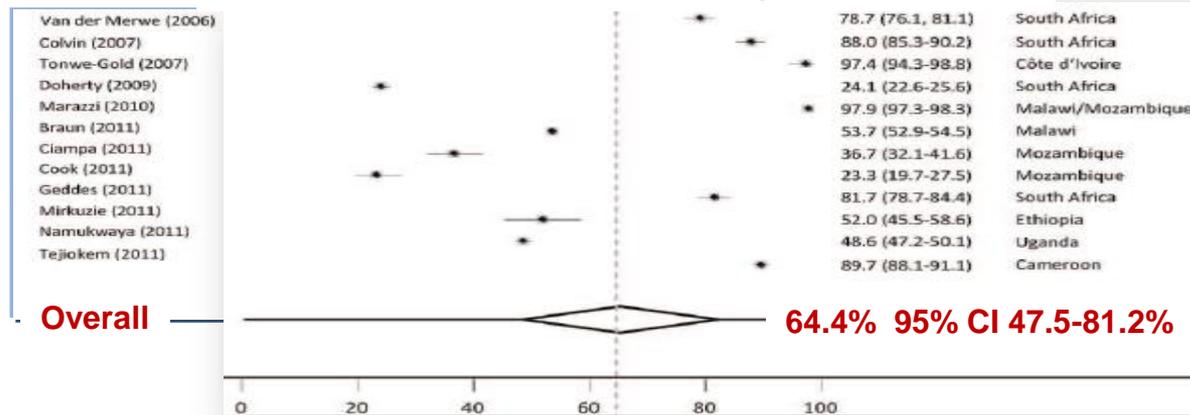
- Limited depth of services for the HIV-exposed infant
- Low rate of infant prophylaxis
  - Only 43% of HIV exposed infants received ARV prophylaxis in 2010
- Weak systems for infant follow-up
  - 8% of HIV-exposed infants born initiated cotrimoxazole prophylaxis by 2 months of age (2008)
  - Final infection status rarely determined after weaning
  - Infant feeding guidance difficult to implement, associated with poor outcomes



# PMTCT Doesn't End at Delivery

Systematic Review and Meta-Analysis-Wettstein C et al. AIDS 2012 Aug 21 (epub)

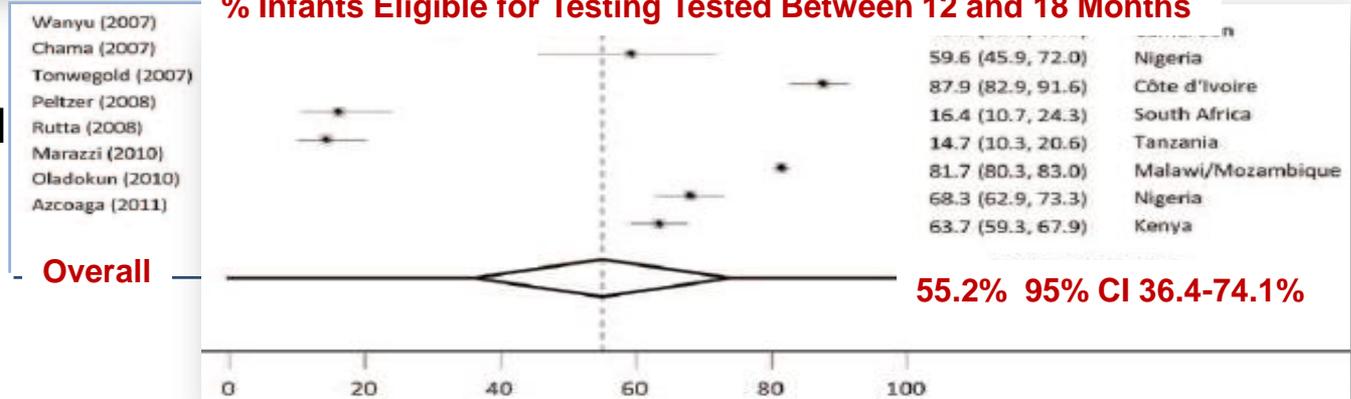
## % Liveborn Infants Tested for HIV by PCR at 6 Weeks



In 12 studies, only ~2/3 of HIV-exposed infants returned for diagnostic testing at age 6 weeks.

In 7 studies, only ~55% of HIV-exposed infants returned for final diagnostic testing at age 12 to 18 months.

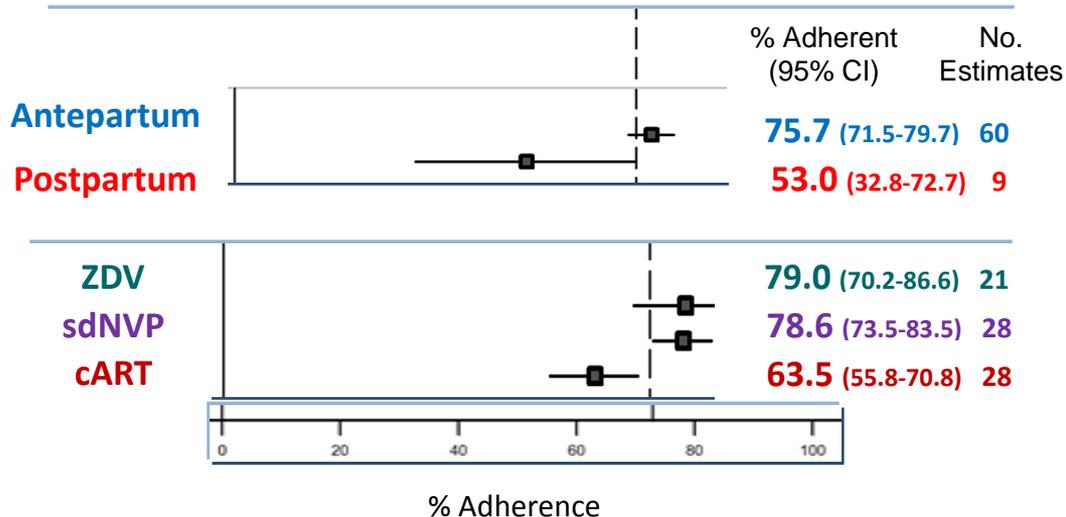
## % Infants Eligible for Testing Tested Between 12 and 18 Months



# ART Adherence During Pregnancy and Postpartum

*Nachega J et al. AIDS 2012;26:2039-52*

- Meta-analysis 51 studies in 20,153 pregnant women.
- Adequate adherence defined as >80% adherence to doses.
- Overall, only 73% reported >80% adherence.

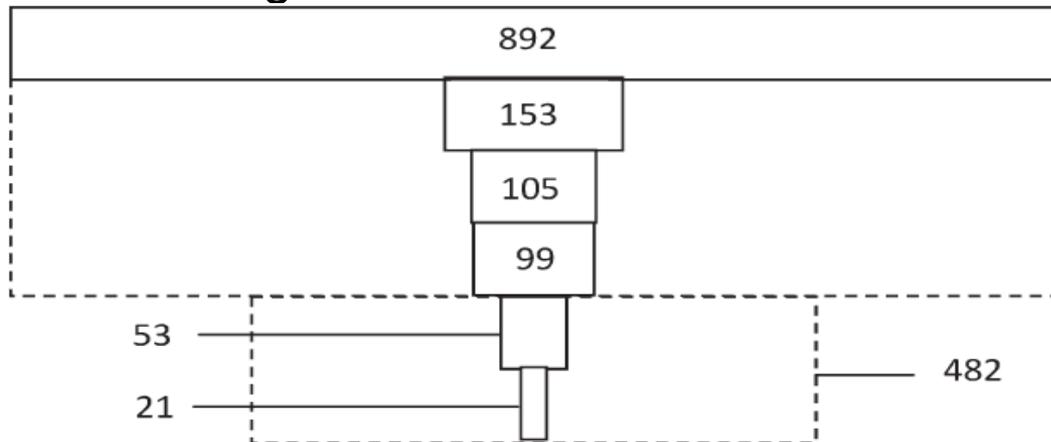


- Adherence was significantly worse in the postpartum period
- Adherence was significantly worse in women receiving cART.

# Poor Linkage to Ongoing Care for HIV-Infected Pregnant Women in Kenya

*Ferguson L, et al. JAIDS 2012;60:e90-7*

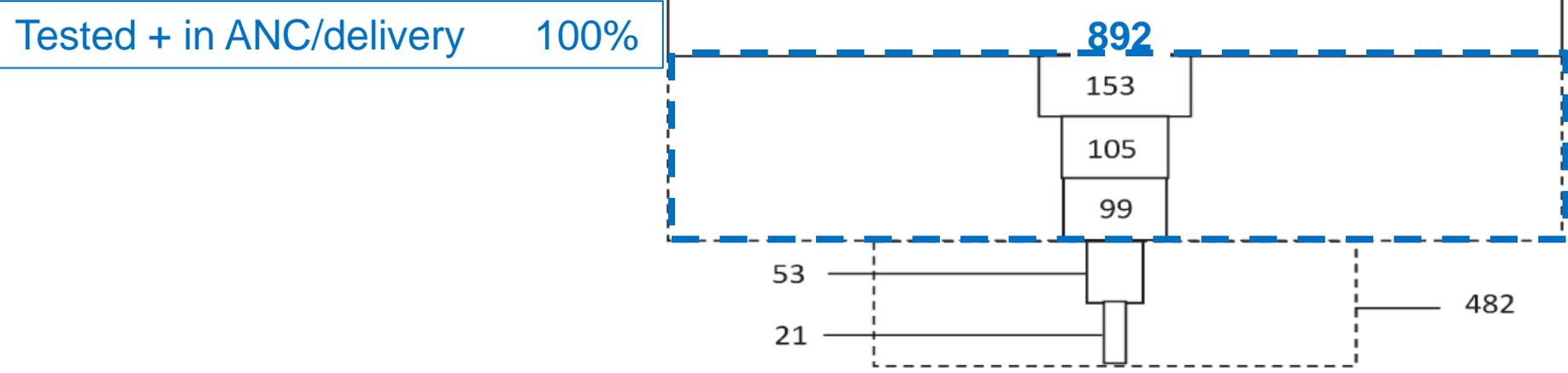
Attrition in the Cascade of HIV Assessment and Treatment for Women Identified as Infected through PMTCT Services



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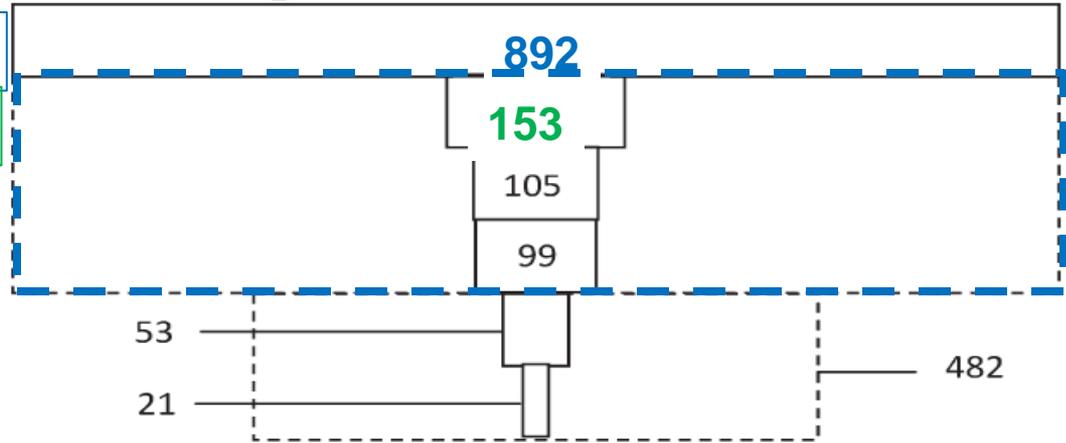
If no drop out, all 892 women would have registered and had CD4

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Tested + in ANC/delivery	100%
Register HIV clinic c/in 6 mo	17%



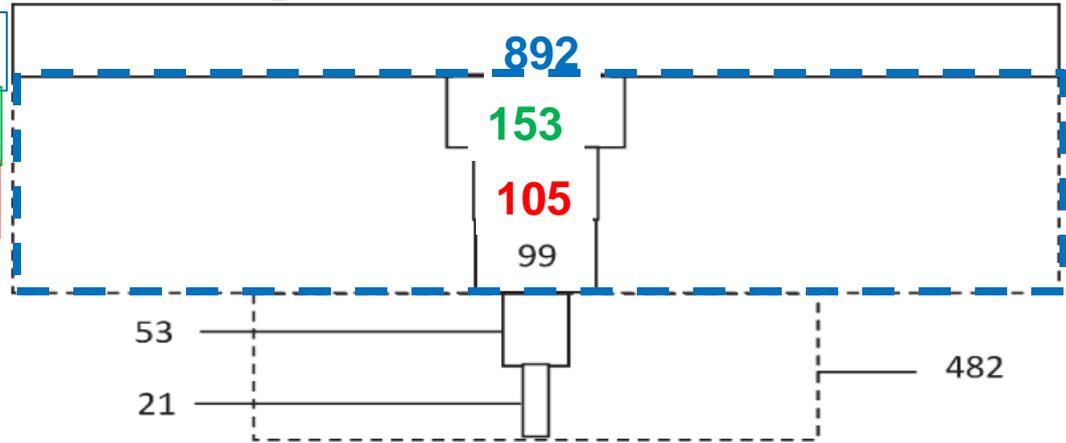
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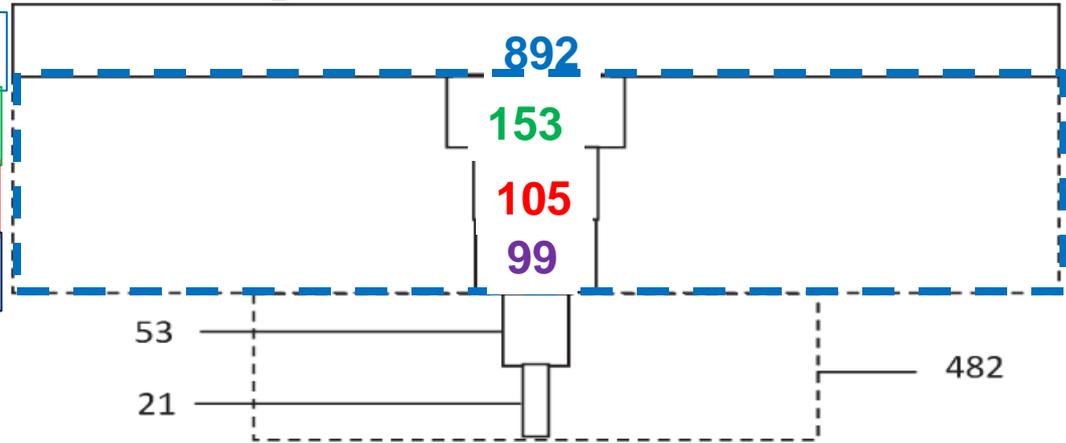
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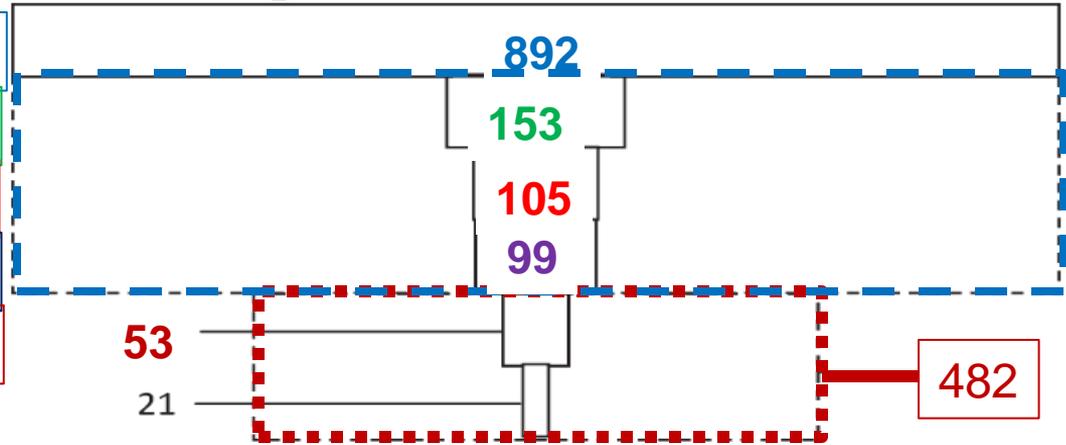
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Register HIV clinic c/in 6 mo	17%
Return for 2 <sup>nd</sup> visit	69%
CD4 count done	68%
Needed ART (CD4<350)	54%

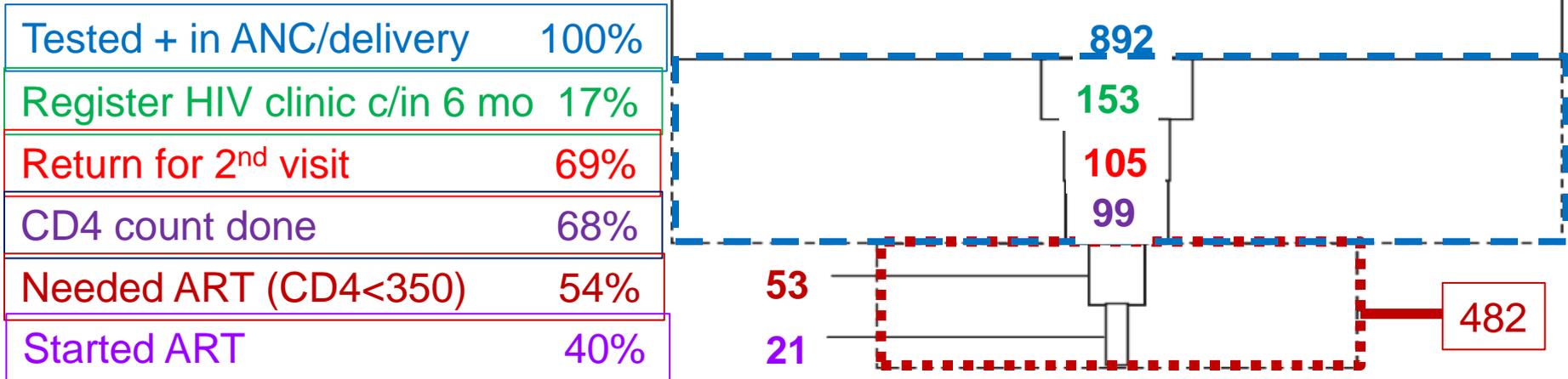


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Of these 482 (54%) would have been eligible and started ART

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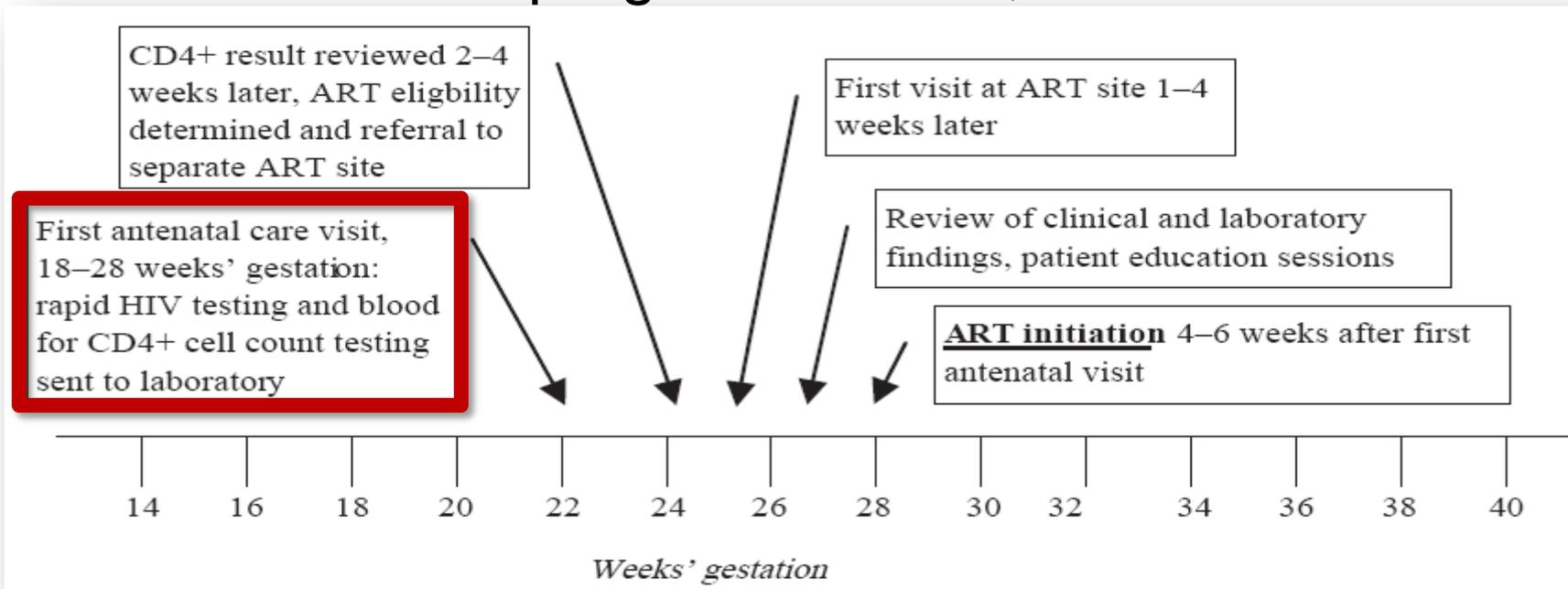


If no drop out, all 892 women would have registered and had CD4  
Of these 482 (54%) would have been eligible and started ART  
Only 21 actually started ART

# Can We Improve ART Initiation in Pregnant Women?

Myer L et al. *AIDS Care* 2012;24:986-92

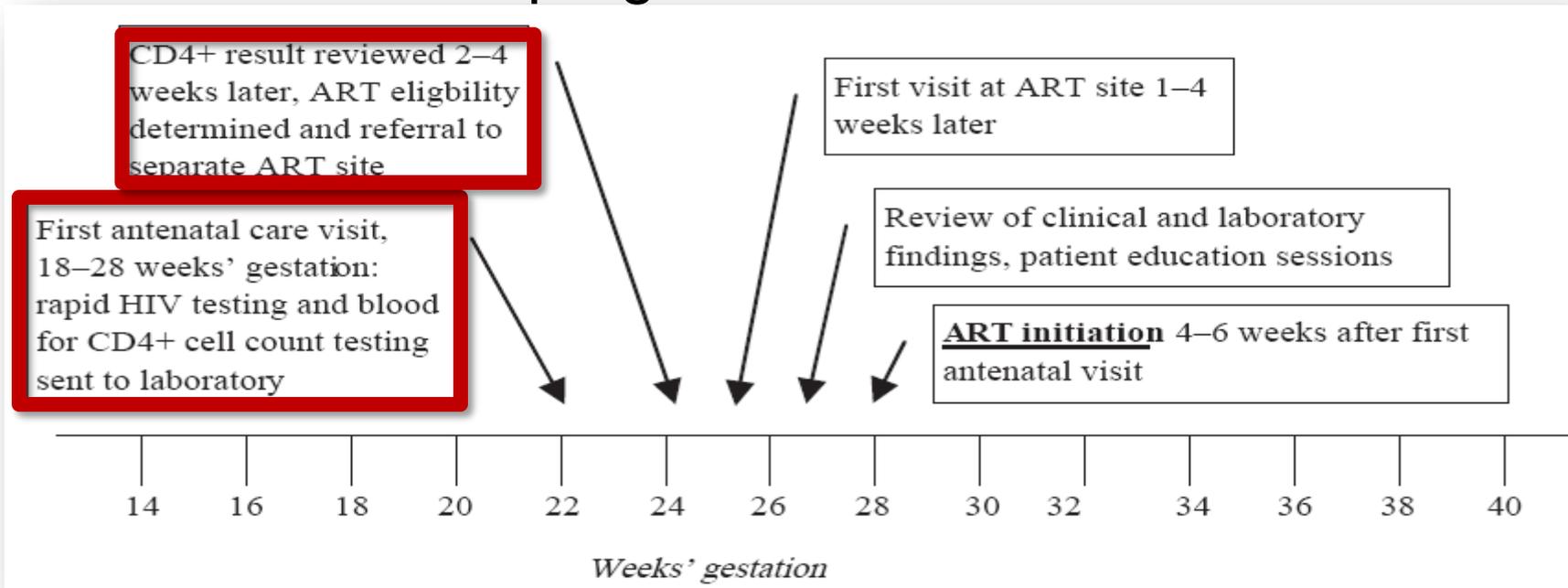
## Current standard of care for ART initiation in HIV-infected pregnant women, South Africa



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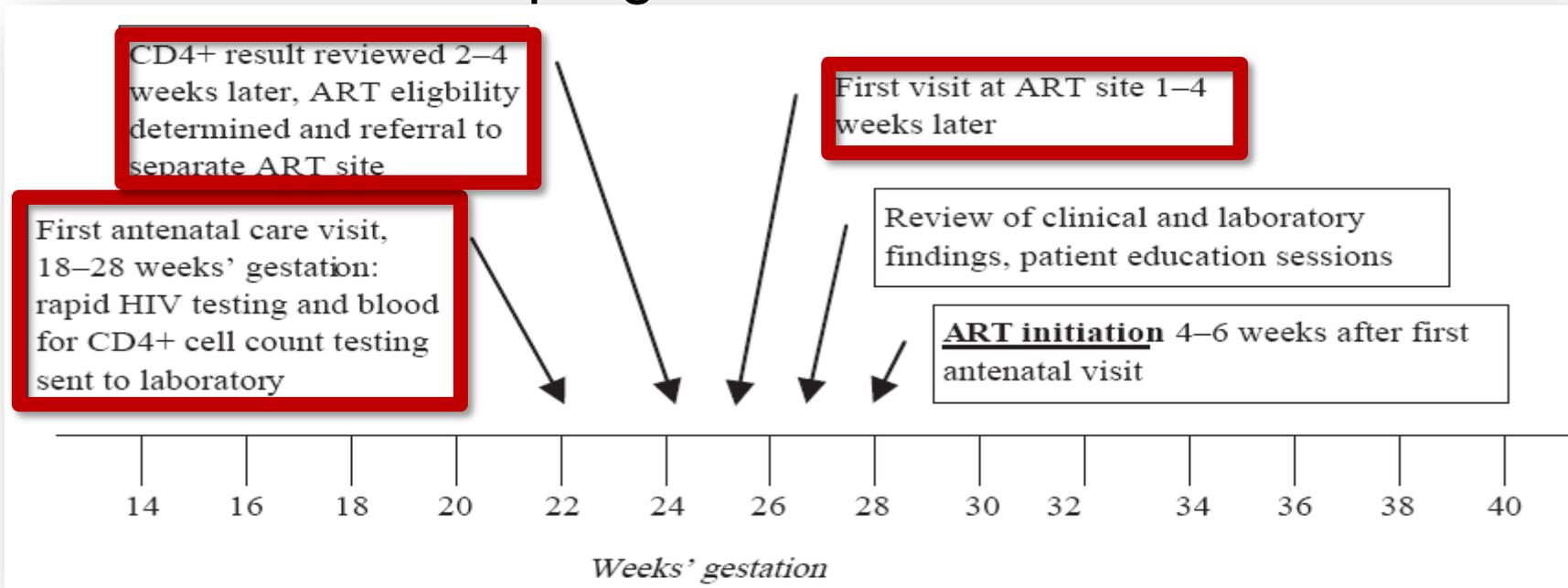
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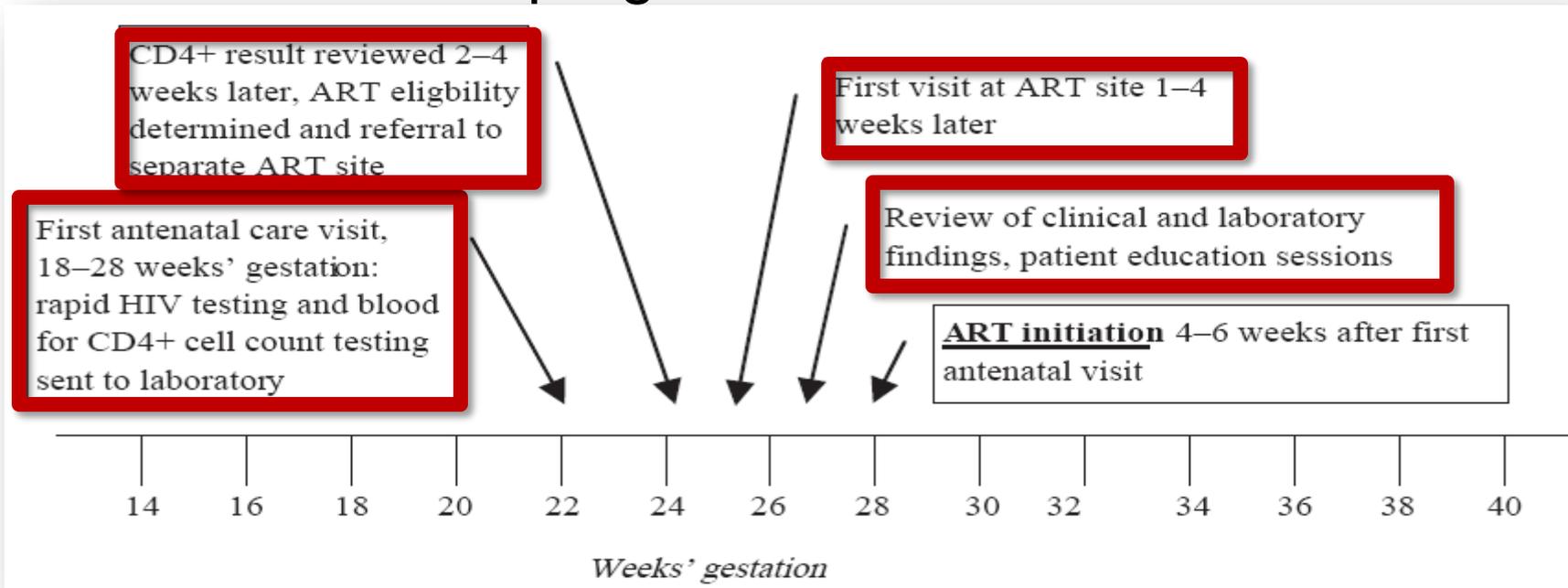
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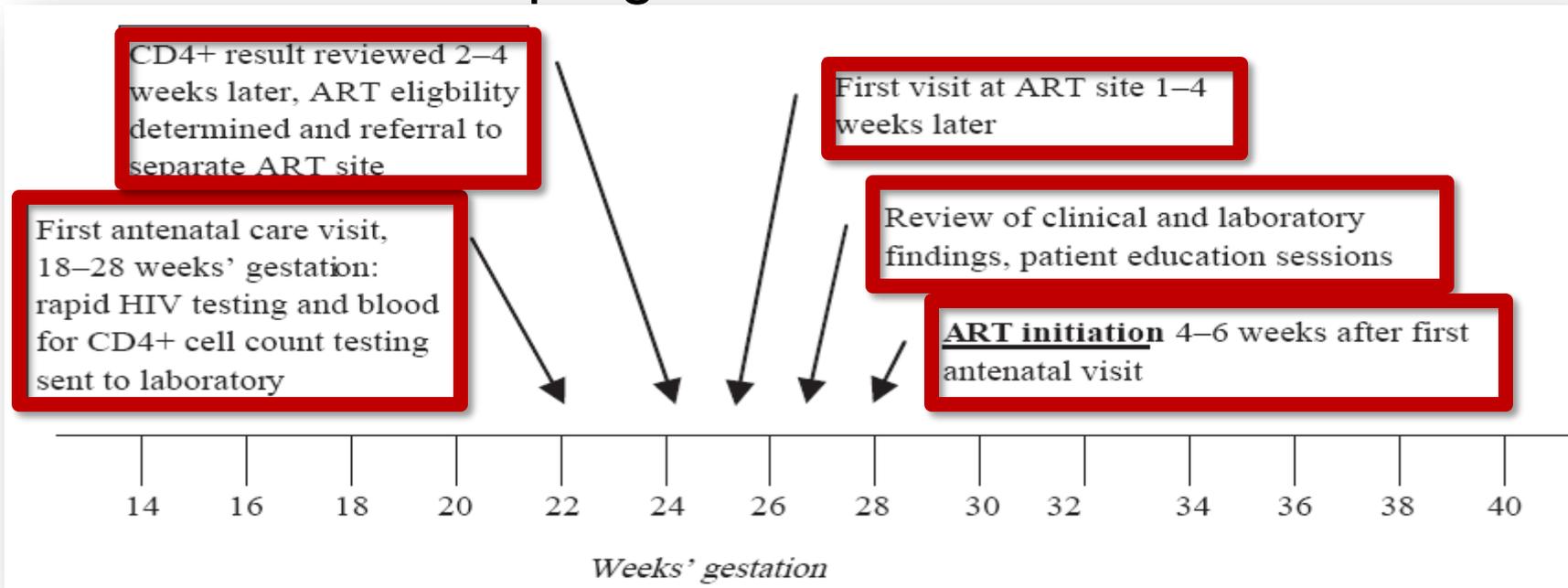
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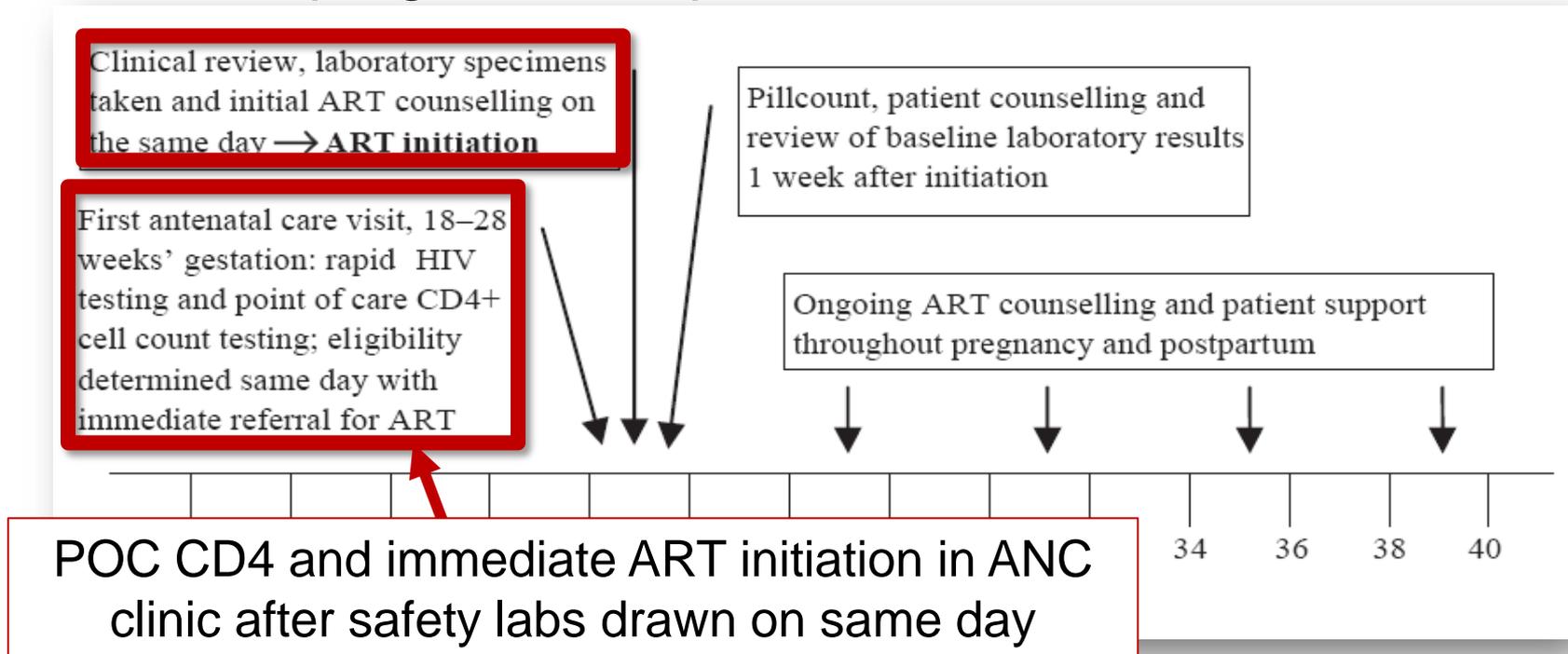
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# Promising Practices: Pilot Program for Rapid Initiation of ART in Pregnant Women, Cape Town

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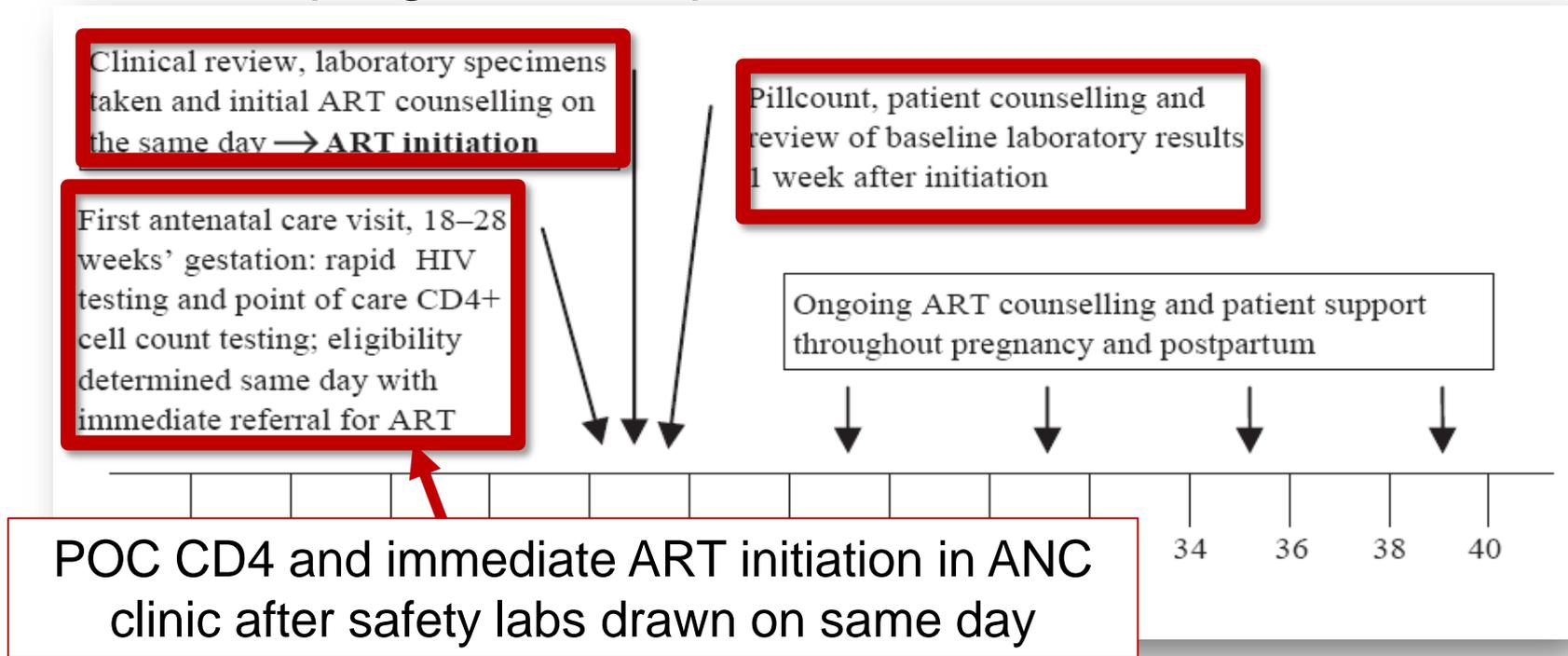
## Pilot program for rapid ART initiation in ANC



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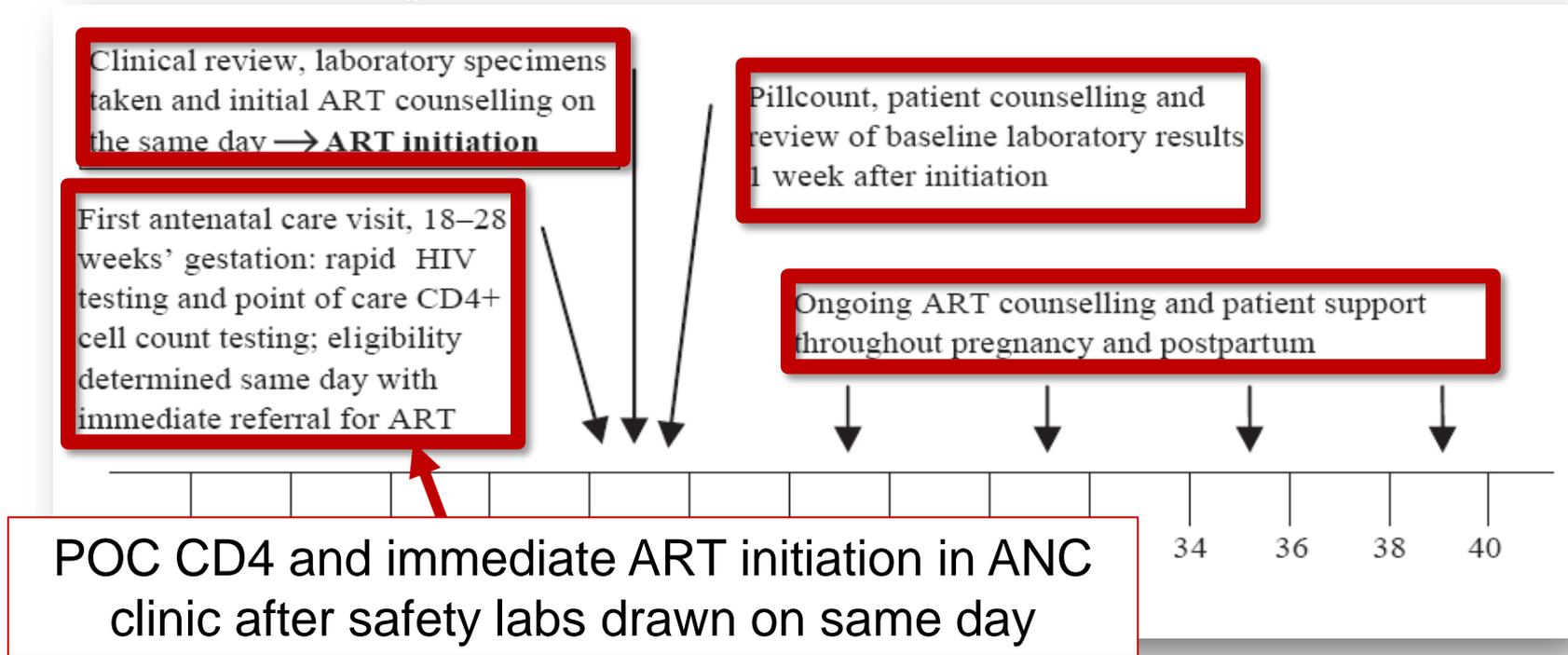
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## Pilot program for rapid ART initiation in ANC



# Promising Practices: Pilot Program for Rapid Initiation of ART in Pregnant Women, Cape Town

*Myer L et al. AIDS Care 2012;24:986-92*

## Pilot program for rapid ART initiation in ANC

- Between Feb-Aug 2011, 221 HIV-infected women referred to program; 101 (46%) eligible for ART
- 98 (97%) started ART, 89 (91%) on same day as diagnosis

POC CD4 and immediate ART initiation in ANC clinic after safety labs drawn on same day

34 36 38 40

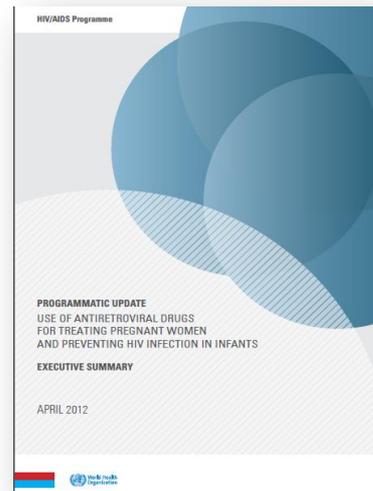
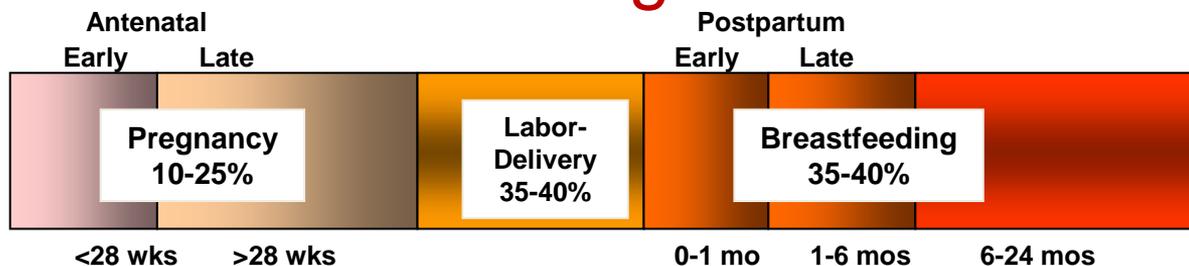


## Prevention of mother-to-child transmission of HIV and the health-related Millennium Development Goals: time for a public health approach

Erik J Schouten, Andreas Jahn, Daliso Midiani, Simon D Makombe, Austin Mnthambala, Zengani Chirwa, Anthony D Harries, Joep J van Oosterhout, Tarek Meguid, Anne Ben-Smith, Rony Zachariah, Lutgarde Lynen, Maria Zolfo, Wim Van Damme, Charles F Gilks, Rifat Atun, Mary Shawa, Frank Chimbandira

*Lancet* 2011;378:282-4

# Proposed “Option B+”: Life-Long ART for All Pregnant Women



Maternal Lifelong ARV Treatment (ART) for ALL HIV-Infected Pregnant Women

# Benefits of Option B+



## OPTION B+ Maternal Lifelong ARV Treatment (ART) for ALL HIV-Infected Pregnant Women

- Easier to implement when CD4 availability limited; assures women who need ART get appropriate regimen
- Use of once daily TDF/3TC/EFV simplifies administration and harmonizes with adult recommendation
- Reduce MTCT
- Avoid stop-start with repeat pregnancies (“protection from conception” for future pregnancies)
- Reduces sexual transmission in discordant partners, assuming good adherence and maintenance of viral suppression

# Uncertainties of Option B+



## OPTION B+ Maternal Lifelong ARV Treatment (ART) for ALL HIV-Infected Pregnant Women

- Limited ARV safety data for TDF/EFV in pregnancy especially in populations with underlying malnutrition/comorbidities; conflicting data on triple ARV and preterm delivery
  - Critical need to assure pharmacovigilance surveillance
- Acceptability and adherence
  - Special attention needed - resistance if not adherent (and assumed benefits PMTCT and sexual tx will not accrue)
- Need for trained staff/task shifting from MDs to administer drugs
- Drug costs/equity

# Summary: Opportunities and Challenges in PMTCT

---

- Great success story in well resourced settings.
- Incomplete success in low and middle income countries.
- Virtual elimination will require expansion of ART in antenatal setting as well as more effective strategies for implementation and greater use of more potent regimens.
- Efforts to simplify strategies and expand ART to all pregnant women have potential to reduce the number of new pediatric infections and improve maternal health outcomes.

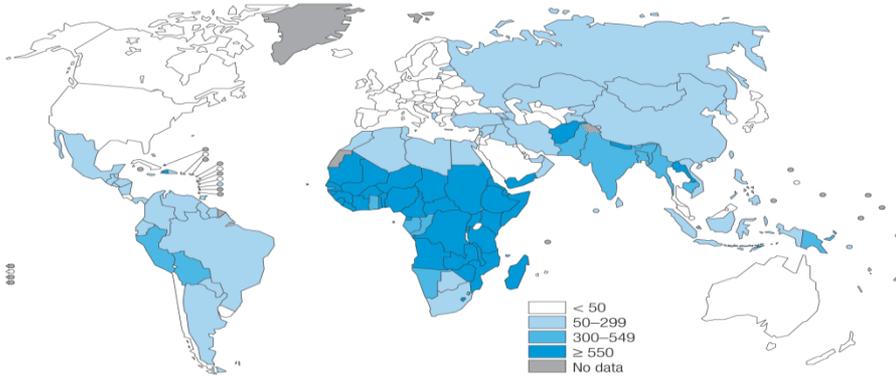
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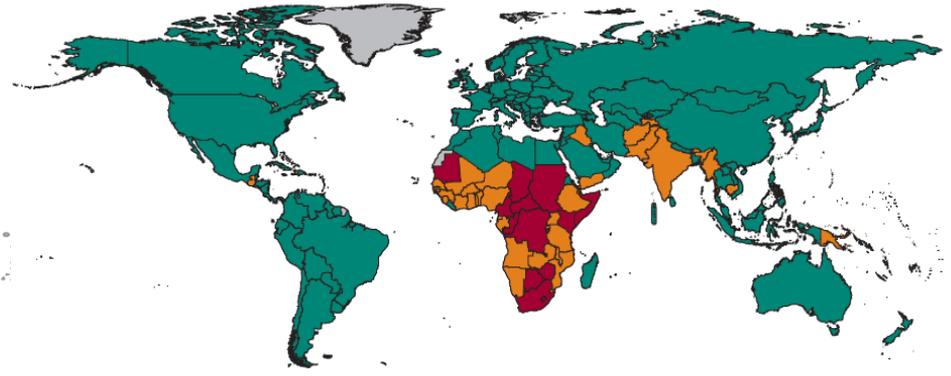
- ARVs alone, whether Option A, B or B+, will not eliminate MTCT; multiple programmatic changes are required.
- Rationale for Option B and B+ include apparent simplicity, multiple pregnancies, maternal health, and decreasing sexual transmission in discordant couples.
  - Retention of women in care is an essential component.
  - Adherence and continuous viral suppression are key.
  - Family planning needs must be met to eliminate MTCT.
  - Surveillance for maternal and infant safety of these strategies will be important as we move forward.

# Challenges but Also Opportunities

## Maternal mortality



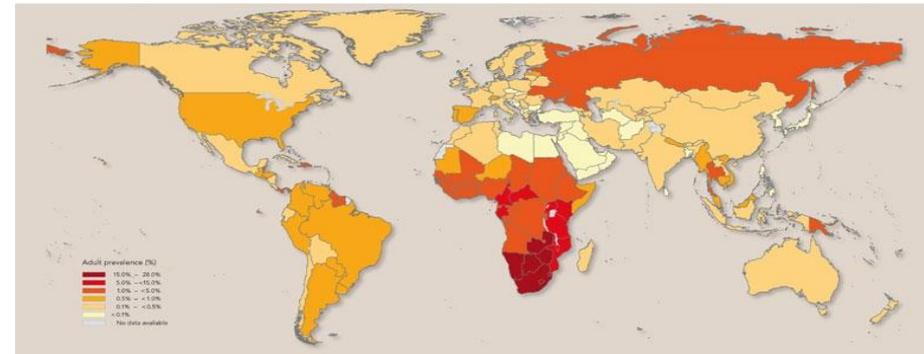
## Under 5 mortality



We have a unique opportunity to build on the PMTCT platform:

- To address other health threats
- Address maternal and child mortality
- Strengthen MCH services
- Ensure good health outcomes for mother, child, and family

## HIV Global burden

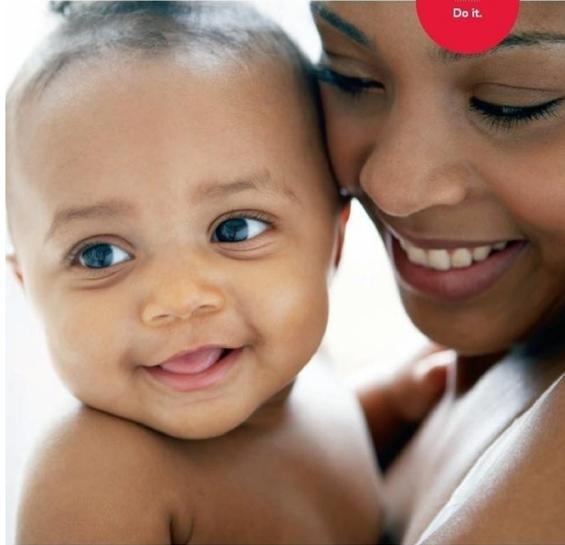


# Thanks For Your Attention

Special thanks to:  
Elaine Abrams

COUNTDOWN TO ZERO

Believe it.  
Do it.



GLOBAL PLAN TOWARDS THE ELIMINATION OF NEW HIV INFECTIONS  
AMONG CHILDREN BY 2015 AND KEEPING THEIR MOTHERS ALIVE  
2011-2015



Working Together for an  
AIDS-Free Generation



S.Varsha, Age 13, India

 WORLD AIDS DAY  
December 1

